AMERICAN COLLEGE OF CLINICAL PHARMACY

PEDIATRIC Pharmacotherapy

Sandra Benavides, Pharm.D., and Milap C. Nahata, Pharm.D., FCCP, Editors



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Pediatric Pharmacotherapy

PEDIATRIC
Pharmacotherapy

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Dedication

To my husband, Joshua, and my parents, Sara and Jose, for their endless love and support; my mentors James and Milap for igniting and molding my passion for pediatrics and teaching; and finally to my sons, Joshua and Jude, … for reminding me every day what really matters in life.

S. Benavides

I dedicate this work to my students and fellows, patients and caregivers, colleagues and collaborators, mentors and friends, and family in the United States and India for their inspiration, affection, and support.

M. Nahata

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Preface

The pediatric population is distinct from the adult population. The uniqueness of neonates, infants, children, and adolescents is beyond the physical and developmental distinctions. Consequently, drugs behave differently in this population. Medications may not be absorbed, distributed, metabolized, or eliminated in the same manner as in adults, and the pharmacokinetics may vary across the age continuum from birth to adolescence. Furthermore, medications may have altered pharmacodynamics in children compared with adults, causing increased or decreased efficacy or safety—about which much is still unknown.

As pediatric clinicians, we are faced each day with challenges in selecting the appropriate pharmacotherapy for children and adolescents. Yet until now, there has been no resource to guide the aspiring pediatric pharmacist in selecting the best pharmacotherapeutic approach. In this book, we focused on common pediatric illnesses and conditions and sought content experts to create chapters geared toward a pharmacy student, a PGY1 resident, an early practitioner, or an adult practitioner occasionally caring for a pediatric patient. The contributors to this book strove to offer essential knowledge of each topic, together with a detailed description of pharmacotherapeutic options. As educators, we understand the need to provide a concise, easy-to-understand, yet thorough resource that allows the reader to glean the most salient points. This book was written, reviewed, and edited by leading clinicians and educators. It presents an overview of disease pathophysiology, clinical features, clear goals for therapy, and insightful treatment considerations based on primary literature, clinical guidelines, and extensive clinical experience.

Our vision in creating this book was to assist the student, resident, and relatively new practitioner in learning about the unique intricacies of the pediatric patient and pediatric pharmacotherapies. For students using this textbook in a pediatric elective or advanced pharmacy practice experience, we hope it will spark their interest in pursuing practice in this dynamic and rewarding specialty. For the PGY1 resident gaining experience in a pediatric rotation, we hope it will be used as an initial point of reference to understand an approach to treating patients. Those early in their careers, or only occasionally caring for pediatric patients in any setting, will perhaps be inspired to learn more about the use of medications in children. Our overarching intent was to empower the book's readers to positively affect the care of the pediatric population.

Acknowledgments

The editors would like to thank the dedicated editorial board members for sharing our vision for this book and contributing in many ways, including selection of content, author and reviewer identification, and writing, reviewing, and editing chapters. Each of the editorial board members brought a unique talent and complementary expertise to this project, which resulted in this comprehensive resource for students and young practitioners.

We would like to acknowledge the time and work invested by the authors, particularly for their diligence to the revisions that came from the reviewers, editorial board members, editors, and the medical editor. We appreciate the time given by each of the experts who reviewed chapters to ensure that the most current and relevant issues were clearly presented by the authors. We know the time devoted to complete these tasks was usually taken away from other activities, responsibilities, and family, and we are grateful for the sacrifices.

The realization of this book would not have been possible without the guidance and organization of the project manager, Janel Mosley. She single-handedly managed the communication between the editorial board members, authors, and reviewers. Janel's devotion to the success of the project and her unwaveringly positive outlook were priceless. Thank you, Janel.

Thank you also to Kimma Sheldon, the medical editor, for the attention to detail in the copyediting process and also to Jen DeYoe, the desktop publisher, for designing the cover and layout of the book. Janel, Kimma, and Jen committed countless hours behind the scenes editing and reviewing each individual chapter, which the editors appreciate.

Numerous students assisted the editors in reviewing and providing feedback on the chapters. Although we could not have captured the names of all the students who contributed to the book, their insight and feedback were valued.

The mission of the American College of Clinical Pharmacy (ACCP) is "to improve human health by extending the frontiers of clinical pharmacy." The College has been instrumental in promoting clinical pharmacy through research, practice, and education. Throughout the creation of this book, we stayed true to the vision of ACCP in creating a text to teach pharmacy students, residents, and new practitioners about the uniqueness of pharmacotherapy in pediatric patients. We are grateful to ACCP for their enthusiastic support of this project.

Finally, thanks to all the practitioners who care for children on a daily basis and to those who contribute to the literature through original research, review articles, and case reports. Without these clinical experiences and publications, our vision would have never been accomplished.

Pediatric Pharmacotherapy

PART I

Introduction

Michelle Condren, Pharm.D., AE-C, CDE

Section Editor

CHAPTER 1

Introduction to Pediatrics

Hanna Phan, Pharm.D., BCPS; and
Milap C. Nahata, Pharm.D., FCCP

Learning Objectives

1. Define the different age groups and corresponding developmental milestones in pediatric patients.
2. Describe differences in vital signs and laboratory normal values based on age.
3. Describe fundamental differences between pediatric and adult patients regarding drug therapy, including availability of treatment options, clinical data, and administration challenges.
4. Define off-label medication use and its implications in pediatric drug therapy.
5. Apply general pharmacotherapeutic concepts and pediatric-specific factors toward providing care and education to patients and families.

List of Abbreviations

AAP	American Academy of Pediatrics
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
GFR	Glomerular filtration rate
PD	Pharmacodynamics
PK	Pharmacokinetics
WHO	World Health Organization

The Role of a Pediatric Pharmacist

Pediatric patients are not simply "smaller adults"; they make up their own population with a need for specialized patient care (Reference 1). Pediatric pharmacy practice focuses on the provision of safe and effective drug therapy in infants, children, and adolescents. As such, the American Society of Health-System Pharmacists (ASHP) recognizes the specialized nature of pediatric pharmacy practice through its statement regarding pediatric pharmaceutical services and its accreditation of specialized postgraduate training programs in pediatric pharmacy practice (References 2–4). The Pediatric Pharmacy Advocacy Group (PPAG) composed a response in support of the ASHP statement. Also noteworthy are the PPAG position statements regarding pediatric pharmacy practice, including the role of pediatric pharmacists in personalized medicine and clinical pharmacogenomics (References 3, 5, 6). The American College of Clinical Pharmacy (ACCP) also supports pediatric pharmacy practice through the Pediatric Practice Research Network and contributions such as the opinion paper about pediatric pharmacy education and training (Reference 7). Drug selection and use, monitoring of effectiveness and toxicity, prevention of medication errors, patient/caregiver education, and contributions to knowledge through research are among the responsibilities of pharmacists when caring for pediatric patients (Reference 8). Likewise, other professional organizations support the role of pharmacists in pediatric patient care. The American Academy of Pediatrics (AAP) acknowledges the importance of interdisciplinary teams in pediatric patient care. In fact, the AAP recommends that prescribers use pharmacist consultation, when available, including the integration of clinical pharmacists in patient care rounds and activities that involve reviewing medication use procedures and orders (Reference 9).

Pharmacists who care for pediatric patients should possess knowledge regarding disease states and drug therapy as well as the skills to apply this knowledge to practice. Pediatric practice includes a wide range of patient ages, with conditions varying from lower respiratory tract infection to trauma. Chronic disease states include lifelong or long-term diseases, such as type 1 diabetes mellitus, asthma, or congenital heart disease. This introductory chapter provides a broad discussion of pediatric drug therapy considerations, whereas subsequent chapters further discuss specific pediatric illnesses and their treatment strategies.

Classification of Pediatric Patients

Pediatric patients are a specialized patient population. Their ages are expressed in days, weeks, months, or years. General classification is often age-dependent. Neonates are the patients from birth to younger than 28 days (4 weeks) of life when born full term, whereas infants are those 28 days to younger than 12 months. Children are often defined as 1–12 years of age. Adolescents can vary in definition, but they are most often recognized as age 13–17 years. Some government agencies combine adolescents with young adults who are up to 24 years of age (References 1, 10–12). Additional classifications are based on other factors such as birth weight and gestational age. For example, "low birth weight" is defined as having a birth weight between 1500 and less than 2500 g, and

"premature" is defined as being born before 37 weeks of gestational age (see Introduction to Neonatology chapter) (Reference 10). An appreciation of the classification of pediatric patients is important in guiding medication selection because some medications are contraindicated for patients of certain ages. Medication dosing can also be affected by such classifications because dosing may depend on organ function (e.g., kidney or liver) development, which progresses with age. For example, neonates and infants lack the ability to metabolize alcohol by alcohol dehydrogenase, whereas adults have this ability. Thus, the use of elixir formulations should be avoided whenever possible in infants (Reference 13).

Uniqueness of Pediatric Pharmacotherapy

Pediatric patients are unique because of their differences in regards to pharmacokinetics and pharmacodynamics (PK/PD), psychosocial influences on drug therapy selection, and treatment options from their adult counterparts. Developmental changes in PK/PD affect drug therapy selection and dosage requirements in the pediatric age continuum, from birth to 18 years (see Pediatric Pharmacokinetics chapter). Pediatric clinicians must also consider factors that affect caregiver medication administration hesitance. These include cultural beliefs, socioeconomic status, and psychosocial differences among age groups (e.g., child vs. adolescent). Pediatric patients also require special consideration when using specific drug formulations. For example, because children younger than 6 years are generally unable to swallow solid dosage forms, oral liquids are preferred for this younger age group.

Off-label use occurs often because of the limited availability of U.S. Food and Drug Administration (FDA)-approved indications for this patient population. From 67% to 96% of outpatient prescriptions and about 79% of inpatient admissions involve off-label medication use in the United States (References 14, 15). With limited evidence-based data (e.g., randomized controlled trials) available for many needed medications, selection and dosing of pediatric drugs is a considerable obstacle for health care professionals. Pharmacists who specialize in pediatrics are an important and integral part of the patient care team, both in the outpatient and inpatient care settings, because they are equipped with skills to evaluate drug information and possess specialized knowledge about developmental PK/PD (Reference 7).

Epidemiology of the Pediatric Population

The pediatric population accounts for almost one-third of the U.S. population, as well as those of other nations such as Canada (References 16, 17). Although chronic illnesses primarily occur in adult patients, patients younger than 17 years also face many chronic conditions, with more than 10 million suffering from asthma and 5 million from attention deficit-hyperactivity disorder in the United States (Reference 18). Although long-term or chronic medication use is often associated with adults, especially the elderly, more than 14% of children (9.5 million) in the United States take a prescription medication chronically for at least 3 months during a year (Reference 18).

Infants, children, and adolescents compose a considerable proportion of the patients in a variety of health care settings, including community pharmacies, clinics, emergency departments, and hospitals. With almost 26 million ambulatory care visits in a 10-year period (1997–2007) among 0–24 year olds compared with about 14 million among those 65 years and older, this younger patient population uses a considerable number of outpatient health care resources (Reference 19). Overall, hospitalization rates of pediatric patients younger than 15 years (about 358 per 10,000 population in 2007) are often lower compared with adults 45–64 years of age (about 1100 per 10,000 population in 2007) (Reference 20). However, greater than 20 million emergency department visits occurred among pediatric patients younger than 15 years, compared with 24 million visits among adults who were 45–64 years of age in 2007. These data emphasize a continued need for pediatric-specific care, especially drug therapy (Reference 21).

Growth and Development

Infants and children are often monitored for growth and development. Markers of physical growth include weight, length or height, head circumference, weight-for-length, and body mass index (BMI). These markers are age- and sex-dependent; therefore, the use of correct tools for measuring pertinent parameters on the basis of these factors is important for proper nutritional status and the physical growth assessment of pediatric patients. For children younger than 2 years, the World Health Organization (WHO) growth charts are recommended to assess these parameters (Figure 1). Since breastfeeding is the recommended standard for infants by the Centers for Disease Control and Prevention (CDC), the WHO growth charts reflect growth based on this feeding approach. The WHO growth patterns represent infants who were predominantly breastfed for at least 4 months duration and continue to breastfeed at 12 months of age. The CDC growth charts are recommended when assessing children 2 years and older (Figure 2) (Reference 22). Growth charts provide a graphic representation of a child's growth with respect to the general pediatric population among six countries including the United States. To use these charts, a patient's parameters (e.g., age and BMI) should be plotted

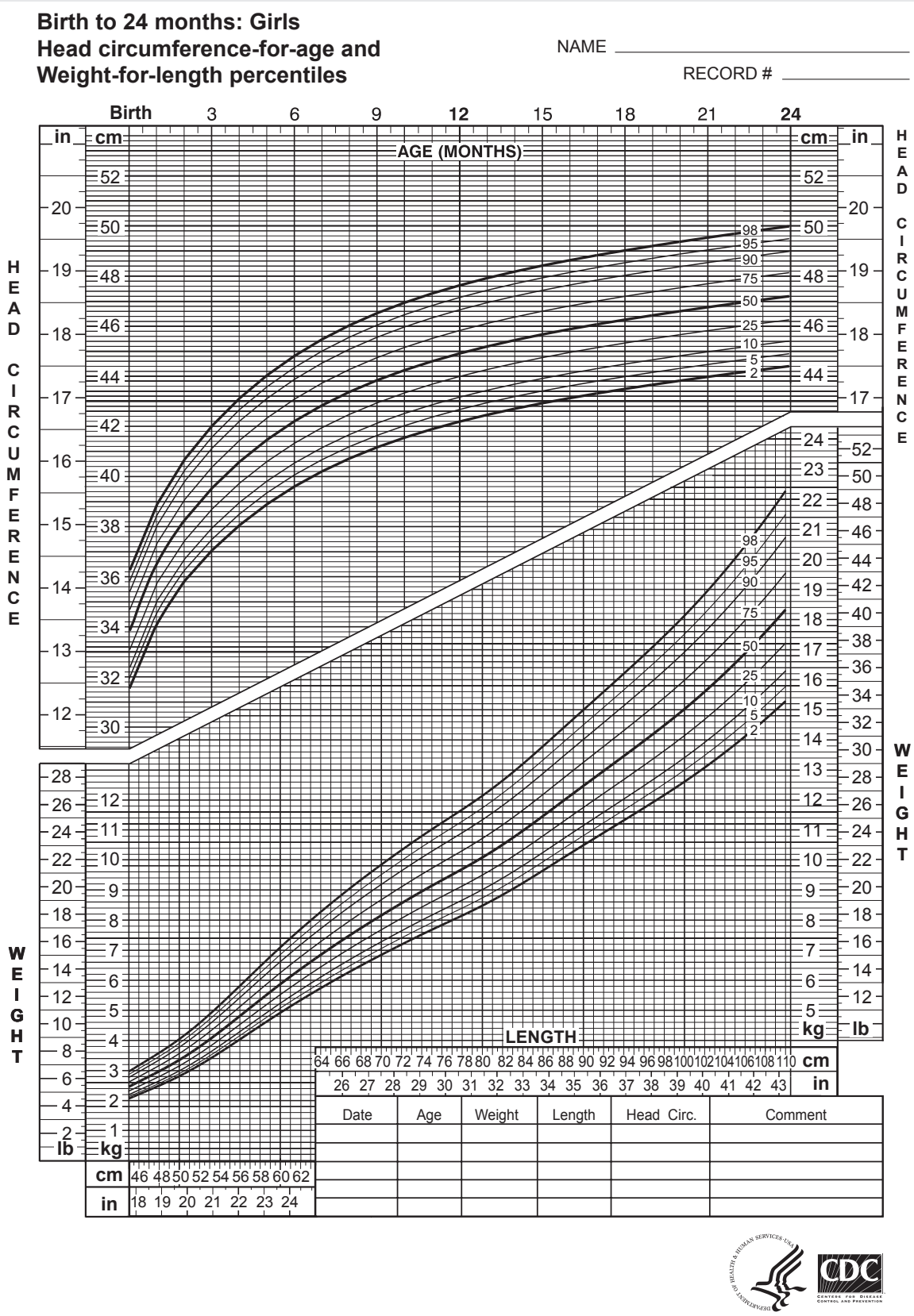


Figure 1. Example of WHO growth chart: girls (age 0–24 months), head circumference-for-age and weight-for-length percentiles (Reference 22).

Reproduced from World Health Organization Growth Standards (www.who.int/childgrowth/en), published by the Centers for Disease Control and Prevention, November 1, 2009.

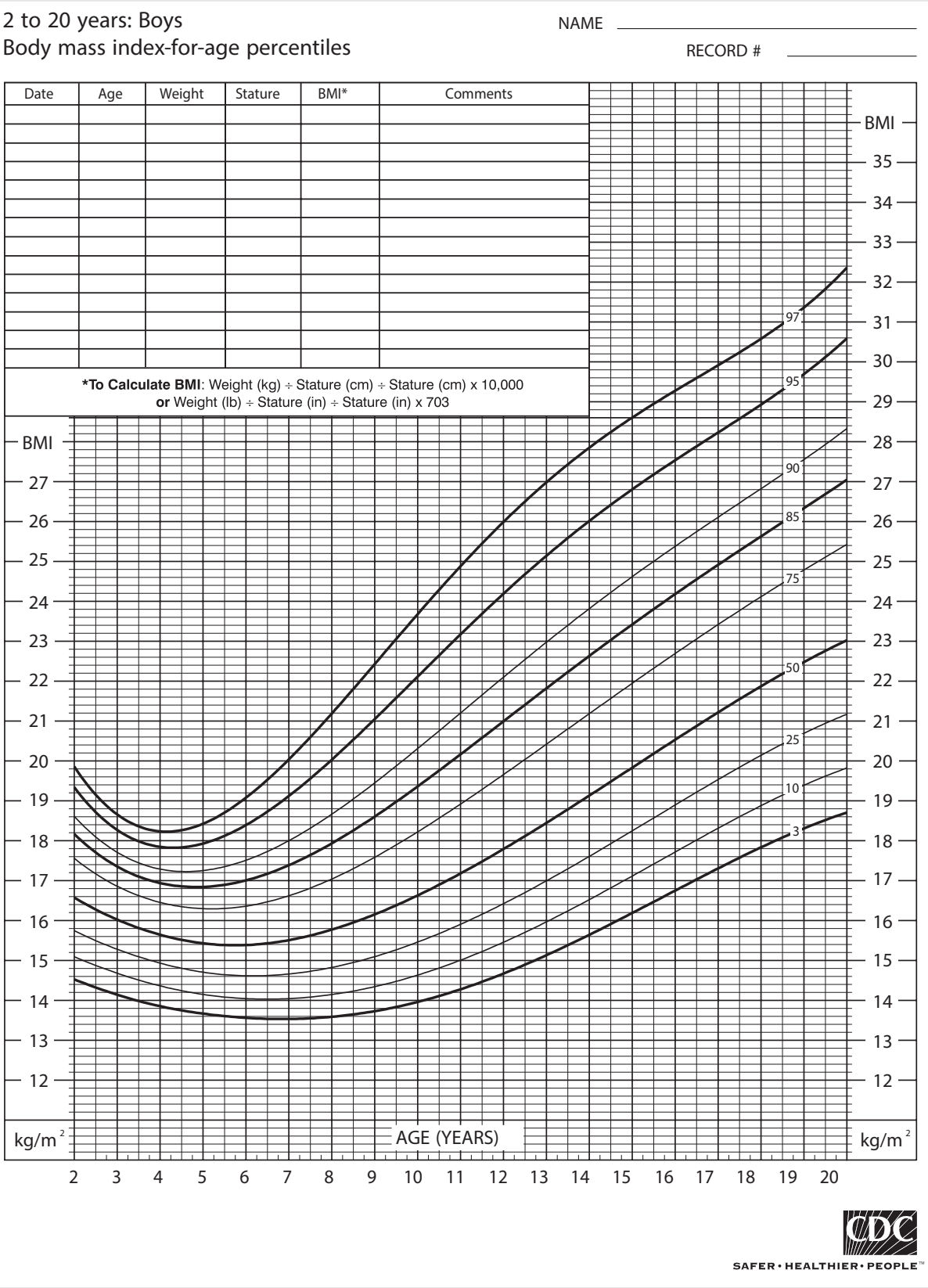


Figure 2. Example of CDC growth chart: boys (age 2–20 years), body mass index-for-age percentiles, 2000 (Reference 22).

BMI = body mass index.

Reproduced from Centers for Disease Control Growth Charts (www.cdc.gov/growthcharts) developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, May 30, 2000 (modified October 16, 2000).

on each axis, finding the cross-coordinate between the two parameters. This point should correlate with a percentile (e.g., 10th percentile) (Reference 22). Nutrition status is often assessed on the basis of growth percentiles (e.g., BMI) (see Parenteral and Enteral Nutrition and Pediatric Obesity chapters). Also noteworthy is the gradual development of organ (e.g., kidney and liver) function and drug distribution space (e.g., total body water) affecting the PK/PD of drugs administered to the patients (see Pediatric Pharmacokinetics chapter).

Motor and cognitive milestones are also important in child development. Motor development milestones involve the ability to perform an activity such as sitting straight or taking first steps. Motor skills can be divided into two classifications. Gross motor skills are often considered large movements; smaller movements often associated with appendages or mouths are considered fine motor skills. Both skill types are monitored closely, especially during the first 2 years of life. Examples of gross motor skills include holding the head steady upright, sitting upright on one's own, beginning to walk, beginning to run, and beginning to jump at 3, 6, 12, 18, and 24 months of life, respectively. Fine motor skills also develop in tandem with grasping toys, transferring objects from hand to hand, grasping with fingers, stacking building blocks, and the ability to hold eating utensils at the same time intervals (References 23–25). These markers of normal physical development from birth to adulthood can affect medication administration. For example, the ability to grasp and hold objects is needed in manipulating and self-administering dosage forms such as metered dose inhalers.

The Piaget stages are often used to describe cognitive development. These stages (sensorimotor, preoperational, concrete operations, and formal operations) span the ages from birth to 18 years and indicate the progression of comprehending language and knowledge (see Communicating with Children, Adolescents, and Their Caregivers chapter) (Reference 26). Cognitive development is of importance in medication administration and education about medications and techniques. Comprehension of language and knowledge can affect one's understanding of medication administration instructions and the importance of treatment. A poor understanding of why and how to take mediations can result in both poor medication adherence and poor patient outcomes. Assessments of growth, motor, and cognitive developmental milestones are recommended during each pediatric preventive care visit, also known as "a well-check visit," to detect developmental delay as early as possible (Reference 25).

Differences in Pediatric Patient Data—Vital Signs, Laboratory Values, and Calculations

Assessment of vital signs, as in adult medicine, is imperative in the evaluation of pediatric patients. Changes in vital signs can be indicative of efficacy and safety in drug therapy. For example, respiratory rate and heart rate can be used as markers of efficacy and adverse reactions from the use of albuterol, respectively. Normal values for heart rate, respiratory rate, blood pressure, and body temperature are different from adult values because of physiologic differences. Pain scores are also an important marker for assessing a pediatric patient and should be considered "vital" in their care. Pain is perceived by patients of all ages, including newborns. Therefore, pain assessment should be part of the routine assessments of pediatric patients. Laboratory values of infants and children also differ from those of their adult counterparts because of physiologic differences, and they should be evaluated appropriately. Different equations are also used to assess pediatric patient data (e.g., creatinine clearance).

Vital Signs

Normal ranges for heart rate and respiratory rate are age-dependent. Blood pressure ranges are not only reliant on age, but also on sex and height percentile (see Pediatric Hypertension chapter). It is important to be familiar with normal ranges and individualized patient data in order to optimize the monitoring of patient outcomes on drug therapy. Reference ranges for heart and respiratory rates can vary by resource and are not necessarily evidence based (Reference 27). The American Heart Association has a set of ranges for heart and respiratory rates as part of the Pediatric Advanced Life Support guidelines. For patients from birth up to 3 months of age, the normal heart rate is between 85 beats/minute and 205 beats/minute, and the heart rate range decreases to 100–190 beats/minute at 2 years of age. The heart rate of children ranges from 80 beats/minute to 140 beats/minute at 2–10 years of age and is closer to that of adults at 60–100 beats/minute among patients older than 10 years. Respiratory rate is similar to heart rate in its downward trend with increasing age, with ranges of 30–60 breaths/minute for infants, 24–40 for children up to 3 years of age, and 22–34 for children around 3–5 years of age. For school-aged children up to about 12 years of age, respiratory rate is between 18–30 breaths/minute and, around adolescence, approaches adult values at 12–16 breaths/minute (Reference 28).

The AAP guidelines provide blood pressure reference ranges for assessment on the basis of age, sex, and height for children 1 year or older. In general, systolic blood pressure at the 50th percentile can range from 80 to 98 mm Hg, 91 to 106 mm Hg, and 99 to 122 mm Hg, and diastolic pressure can range from 34 to 56 mm Hg, 53 to 63 mm Hg, and 59–70 mm Hg at age ranges 1–5, 6–11, and 12–17 years, respectively. For specific ranges based on height percentile, sex, and age, one should refer to the Report on Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Reference 29). Overall, heart and respiratory rates decrease with age, and blood pressure increases with age.

Body temperature can be determined rectally, orally, axillary, and tympanically. Rectal temperature measurement is recommended by the AAP for children younger than 4 years. For older children, oral measurement can be used. Axillary measurement can be used for patients as young as 3 months, although it is thought to be less accurate than oral and rectal measurements. Tympanic measurement is considered potentially less accurate because of cerumen accumulation (References 30, 31). Some institutions use temporal artery thermometry, which is most accurate in patients older than 3 months (Reference 32). In general, the difference in body temperature between rectal, oral, and axillary temperatures, from highest to lowest, is about 0.6°C (1°F).

Fever is a normal physiologic response involving the hypothalamic reaction to pyrogens, and its presence should not be cause for immediate drug therapy treatment in otherwise healthy pediatric patients unless it is accompanied by discomfort. In patients at increased risk of severe infection, the threshold for action is considerably lower, and fever should be evaluated further. In general, with a mean normal temperature considered a reading of 37°C (98.6°F), a low-grade fever is considered a body temperature ranging from 37.8°C to 39°C (100°F–102°F). A high fever, temperature greater than 40°C (104°F), may have greater risk of heat-related adverse outcomes. Antipyretics such as acetaminophen may be given for body temperatures greater than 38.3°C (101°F), measured by any route, if the individual presents with discomfort (Reference 33). The definition of fever can vary depending on the route of measurement and patient age. For example, a rectal temperature of 38°C (100.4°F) in a neonate is considered a fever. In infants up to 3 months of age, the threshold for the definition of fever is higher, up to 38.2°C (100.7°F) (Reference 34). The vital signs for premature and term infants or neonates are discussed in the Introduction to Neonatology chapter.

It is also important to assess pain in pediatric patients. Difficulties in pain assessment are most common among patients with a limited ability to have direct communication, such as neonates or infants and young children. Some older pediatric patients (e.g., critically ill individuals) may be unable to verbally express pain symptoms. In such instances, indicators of pain include physiologic markers, like increased respiratory and/or heart rate and oxygen desaturations, as well as changes in behavior (e.g., grimacing or high-pitched crying). Standardized assessment scales such as the Neonatal Infant Pain Scale (NIPS) and the Face, Legs, Activity, Cry Consolability (FLACC) scale use these physiologic or behavioral indicators for neonates or infants and children up to 4 years of age, respectively (References 35, 36). The Wong-Baker FACES scale, with graphic facial expressions, is often used in children older than 4 years (Reference 37). A visual analog scale, or a numeric pain scale, can be used in older children (e.g., 10 years old) who can verbalize and comprehend number values. Additional information regarding the assessment and treatment of pain can be found in the Pain Management chapter.

Laboratory Values

Normal laboratory values in infants and children can differ from those seen in adults. Physiologic differences account for variation in normal ranges by age and are noted throughout the book in reference to the disease states discussed. With the advances in software technology, laboratories now often report abnormal values with adjacent normal ranges based on the age of pediatric patients. Standard pediatric handbooks or references such as *The Harriet Lane Handbook* or the *Pediatric & Neonatal Dosage Handbook* also serve as resources for normal laboratory values for pediatric patients (References 38, 39).

Calculations

In addition to differences in normal vital signs and laboratory value ranges, calculations used to assess pediatric patients differ from those used for adult patients. Body surface area, BMI, and ideal body weight calculations are sometimes used in the dosing of certain medications and in assessing nutritional status (Table 1) (References 40–44). Creatinine clearance is used to assess a patient's renal function and is applied in dosing when renal dysfunction is present or the patient is taking a potentially nephrotoxic drug. The Schwartz equation is used to calculate estimated creatinine clearance in pediatric patients, including low-birth-weight infants and patients up to 21 years of age (Reference 44). The Cockcroft-Gault and Jeliffe equations have been studied and validated in normal adult populations but should not be applied when evaluating pediatric patients (References 45, 46). Although there is a common approach to estimating glomerular filtration rate (GFR) in pediatric patients, the Schwartz equation has limitations. For instance, the Schwartz equation can potentially overestimate GFR, especially in moderate to severe renal insufficiency, because serum creatinine is a crude marker of GFR (References 47, 48). Thus, alternative methods based on additional factors such as cystatin C or blood urea nitrogen have been proposed to estimate GFR in children with renal insufficiency such as chronic kidney disease (Reference 49). Most of the equations listed (Table 1) apply to infants, children, and adolescents; however, their application is limited in the neonatal population. Assessment methods for neonates and premature infants can be found in the Introduction to Neonatology chapter.

Challenges of Medication Adherence

Medication adherence, defined as the "extent to which patients take (or in the care of younger pediatric patients, are given) medications as prescribed," is a challenge for all patient populations; pediatric patients are no exception to this continued health care issue (Reference 50). Although chronic illnesses, such as asthma and diabetes mellitus, are often associated with a high potential for poor adherence, short antibiotic treatment courses for conditions such as acute otitis media are also worth investigating (Reference 50). Consequences of nonadherence include delayed or absent clinical improvement, worsening of illness, and unnecessary therapy modifications that can lead to adverse clinical outcomes. Medication adherence is often difficult to document in ambulatory care practice environments. Approaches to measuring medication adherence include self-report, clinician's impression, dose count (e.g., pills or inhaler counter), refill verification, and monitoring of serum drug concentrations when appropriate (References 51, 52). Devices such as electronic monitors have been used in research settings. However, these are not commonplace in clinic settings and are cost-prohibitive for routine use at this time (Reference 53).

Nonadherence, often considered adhering to a prescribed therapy less than 80% of the time, is multifaceted in nature. Moreover, identifying approaches to improve adherence is challenging. Reasons for poor adherence include forgetting the time to administer doses, experiencing difficulty with caregiver's and/or patient's personal beliefs, encountering socioeconomic limitations, experiencing adverse drug effects, and having unpleasant or inconvenient medication formulation or schedules, as well as child psychological factors, such as peer acceptance among adolescents. In general, younger children (e.g., younger than 5 years) have greater medication adherence to the treatment of chronic illnesses such as asthma (Reference 52). This is because of caregiver responsibility and action in administering necessary medication in most cases. However, it should not be assumed that all caregivers adhere to prescribed treatment regimens. Caregiver education is imperative with every medication dispensed for a child.

Poor medication adherence is seen in all age groups, from infancy to adolescence. For infants and younger children, the caregiver is the primary individual responsible for administering medications. A reason for poor adherence in this subpopulation is apprehension regarding medication adverse effects. An example is

Table 1. Common Equations Used for Calculations in Pediatric Patients (References 40–44, 64)

Calculation	Equation
Body surface area (BSA)[a]	BSA (m^2) = sqrt [(height × weight) ÷ 3600]
Body mass index (BMI)[a]	BMI = weight ÷ height ÷ height × 10,000
Ideal body weight (IBW)[a]	IBW (kg) = [$(height)^2$ × 1.65] ÷ 1000
Creatinine clearance (CrCl)	Original Schwartz Equation CrCl (mL/minute/1.73m^2) = [k × L] ÷ SCr k = proportionality constant L = length in centimeters SCr = serum creatinine in mg/dL
	Bedside Schwartz Equation (patients younger than 1 year) CrCl = [0.413 × height(in cm)]/SCr (in mg/dL)
Estimation of pediatric dosing when limited pediatric-dosing data are available	Approximate pediatric dose = adult dose × [BSA (in m^2) ÷ 1.73m^2]

Patient type	Value of k
Younger than 1 year and low-birth-weight infants	0.33
Term infant younger than 1 year	0.45
2–12 years (male or female) or 13–21 years (female only)	0.55
13–21 years (male only)	0.70

[a]With height in centimeters, weight in kilograms.

nonadherence to inhaled corticosteroid therapy for asthma because of the fear of growth suppression. Other reasons for nonadherence in this younger population can include the caregiver's inability and unavailability to administer the drugs in a timely manner. Some caregivers may become overwhelmed by their many responsibilities, or confusion may occur regarding who among a child's caregivers is responsible for dosing, resulting in missed doses and poor adherence (Reference 54).

Inappropriate measurements of a medication dose can also affect medication adherence. For example, if a caregiver uses a measuring device to administer a liquid medication that results in larger doses (e.g., a large kitchen spoon), adverse drug effects as well as early therapy discontinuation may ensue. Conversely, if caregivers use a device that provides a smaller amount of medication (e.g., a small dining teaspoon), subtherapeutic dosing and poor patient outcomes with respect to efficacy may ensue. Thus, caregivers should be provided with and educated about proper measuring devices such as oral syringes. Some caregivers may also miss doses because of resistance from the child. As a child gets older and enters early adolescence, responsibility for medication administration moves from the caregiver to the child or adolescent. Approaches to improve medication adherence should address the transition from childhood to adolescence, which involves factors such as peer pressure, perceived invisibility, and potential for oppositional or rebellious behavior (Reference 55).

Different approaches have been suggested to improve medication adherence. Behavioral and educational approaches have received the most emphasis in studies regarding chronic diseases such as pediatric asthma and diabetes mellitus (References 56, 57). Caregiver education regarding medications should be reinforced at several points of health care visits because it is important to enhance the caregiver's understanding of the importance and benefit of completing treatment and the risk of adverse effects. Ease of administration, including palatable dosage forms and the need for less frequent dosing, can help caregivers keep to a treatment schedule. Poor palatability of medication, specifically liquid medications, can negatively affect medication adherence. Despite the lack of extensive research data, clinician and parental experiences have shown the importance of palatability as a target to improve adherence (Reference 52, 54). The use of a reward system and positive reinforcement may aid in decreasing resistance by young children during treatment periods. Empowering older children and adolescents positively with knowledge about their disease may improve self-management of drug therapy and medication adherence (Reference 55).

Off-label Medication Use in Pediatric Patients

Off-label medication use is defined as the use of a medication outside its FDA-approved labeled indication(s). Labeled indication includes the age group in which a medication is used, the disease or illness it treats, and the route of administration. Currently, more than 75% of the drugs approved for use in adults lack dosing, efficacy, and safety data pertaining to pediatric patients (Reference 15). Off-label use is legal and well accepted as long as it is based on appropriate clinical judgment. However, limitations to off-label medication use exist, including the potential for denied insurance provider coverage of the medication. Other limitations to off-label medication use are possible medical liability due to serious adverse effects, limited experience for treatment of a condition or specific age group (e.g., neonates), and limited available formulations for use in young populations. Thus, a strong need remains for additional clinical trials to determine the appropriateness of selecting and dosing medications in the pediatric population.

Regulatory changes have been made to decrease the off-label use of drugs in the pediatric population. The Pediatric Rule, issued in 1994, permitted manufacturers to label drugs for pediatric use on the basis of extrapolated efficacy data and additional PK/PD data specific to the pediatric population when disease and therapy response were considered similar to those of their adult counterparts (Reference 58). Unfortunately, this resulted in only a few well-conducted studies regarding infants and children because of the difficulties involved in predicting dose-response from adult data. The FDA Modernization Act (FDAMA) followed in 1997, offering a financial incentive of 6 months' extended market exclusivity for performing pediatric studies (Reference 59). Because of the FDAMA, additional drugs were assigned pediatric labeling. However, efficacy data were still lacking. In 2002, an incentive-based Best Pharmaceuticals for Children Act (BPCA) was implemented, extending the FDAMA and offering a 6-month extension of patent exclusivity to encourage industry to conduct pediatric studies for branded products labeled only for adults (Reference 60). The Pediatric Research Equity Act (PREA) of 2003 also provided potential requirements for the pediatric assessment of drug applications submitted to the FDA for approval in adults. This assessment includes the potential use and evaluation of risk versus benefit in pediatric patients (Reference 58). The FDA pediatric decision tree, a process whereby agents are evaluated for pediatric study regarding PK/PD, efficacy, and safety, is depicted in Figure 3 (Reference 61). For rare diseases with

an occurrence of 200,000 people or less in the United States, such as inborn errors of metabolism, the Orphan Drug Act provides support in the development of needed treatment (Reference 62).

The BPCA has been effective primarily for the blockbuster drugs to receive 6-month patent exclusivity. Thus, the concern remains when extrapolating adult data to treat pediatric patients for many branded products with a limited market and for generic drugs with no incentives. Extrapolation is challenging because this approach is not always accurate when determining safe and effective pediatric dosing. A wide range of evidence in pediatric drug therapy through the identification of well-designed, appropriate biomedical literature is needed to provide optimal, evidence-based care to the pediatric population. The use of available guidelines, such as those commissioned by the National Asthma Education and Prevention Program and National Heart, Lung and Blood Institute for asthma (Reference 63), is recommended, though their individualized application to specific patients is necessary in patient care.

Because of limited pediatric-specific guidelines for much of drug therapy, use of primary literature is crucial in providing evidence-based care to infants, children, and adolescents. Although randomized, placebo-controlled trials are considered the "gold standard" of primary literature, much of the available literature consists of retrospective cohort studies of the pediatric population. Careful evaluation of these data should guide the applicability of the results in clinical practice. Evaluation of literature includes appropriateness of study design, generalizability to the population at hand, and appreciation for statistical and clinical significance of findings. Furthermore, the use of case reports and case series can provide some data regarding unknown effects of newer drug therapy. However, given the small patient populations in these reports, clinicians should assess the appropriateness of applying them to their own patient(s).

A dilemma with newer adult drug therapy options is that there is no exact, recommended approach to dosing such agents in pediatric patients, especially because the agents have no pediatric indication. Although adult dosing often involves a standard dose for most

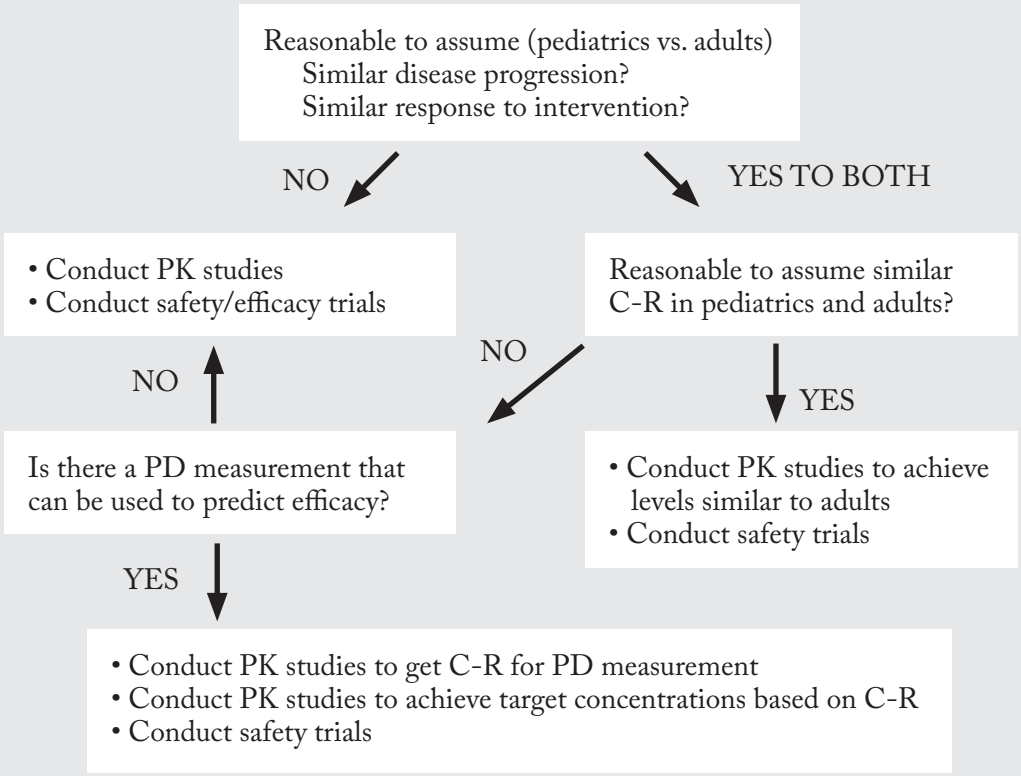


Figure 3. The FDA pediatric decision tree (Reference 61).

C-R = concentration response; PD = pharmacodynamic; PK = pharmacokinetic.
Reprinted from: U.S. Food and Drug Administration: Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications. Available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf. Accessed May 9, 2012.

of the population regardless of age and weight (e.g., omeprazole 20 mg orally daily), pediatric dosing is often weight-dependent (e.g., omeprazole 1 mg/kg orally daily). Pediatric dosages may also be based on age (e.g., neonate vs. child). Rounding of doses is a dilemma not often seen in the care of adults. In pediatric patients, doses of wide-therapeutic index medications (e.g., antibiotics) can be rounded for ease of measurement. Some institutions round doses by 10% to 20%, depending on the risks associated with a given medication.

In the past, approaches to dosing included Fried's Rule, Clark's Rule, or Young's Rule to estimate dosing when pediatric-specific data were not available. However, these equations differentiated a child from an adult by one factor of difference such as age in months or years or weight in pounds. This approach oversimplifies the known complex differences between the pediatric and adult populations. As a result, these approaches can over- or underestimate dosing in pediatric patients. Thus, these methods are no longer recommended for estimating off-label dosing in pediatric patients. If there is no alternative therapy—or if there are limited or no pediatric data for dosing but evidence to support the safety of the drug in pediatric patients—some clinicians may elect to dose on the basis of the body surface area ratio if the child is of normal height and weight for age (Table 1) (Reference 64). However, of note, this method is not a well-studied approach to off-label medication dosing, and caution should be used when considering this option. A potential exists for unaccounted differences in PK/PD between pediatric and adult patients when using this dose-estimating approach, resulting in differences in efficacy and safety. Thus, clinical judgment should be applied when considering off-label medication use and dosing in instances of limited pediatric data.

Medication Safety

Medication errors are preventable events that result from human or system flaws (Reference 9). Pediatric patients are at increased risk of medication errors, with an error rate of 15% of pediatric medication orders compared with 5% of adult medication orders (Reference 9). Prescribing and transcription errors account for many of the medication errors in U.S. neonatal and pediatric intensive care units at 50% of all errors. Because pediatric doses are often calculated (e.g., milligram per kilogram), the risk of calculation error is high. Accuracy and consistency in the units of measurement used are important in preventing calculation and prescribing errors. Decimal errors, such as trailing zeros (e.g., 5.0 mg) and missing leading zeros (e.g., .5 mg), also result in 10-fold or greater errors.

Calculation inaccuracies can lead not only to prescribed dose error, but they can also cause error when medications are compounded into intravenous solutions or oral suspensions. One should also be cautious of potential dispensing errors when the incorrect strength of a medication is selected. Calculation errors can be reduced through computer physician order entry, which can provide automated medication-dosing calculators and mandatory prescription order fields (Reference 65). The use of an alert-based decision support system can potentially prevent several errors; however, it also has the potential to cause "alert fatigue" because of too many unnecessary alerts, which can lead a clinician to bypass warnings for incorrect medication orders. Barcode technology has also helped reduce the incorrect selection and administration of medications (Reference 66). Medication administration error rates have also decreased with the use of technologies such as smart pumps for parenteral medications in daily care (Reference 67). Despite technological advances, however, a potential for human or system error remains during the process of preparing, dispensing, and administering medications. Thus, medication error prevention is a multifaceted task involving the active participation of the health care team as well as the patient and caregiver. Communication between all parties and continued efforts to improve medication use practice are essential in the provision of safe patient care (see Medication Safety chapter).

Fundamentals of Pediatric Patient Care

Application of pediatric-specific knowledge and clinical skills is vital to the successful care of infants, children, and adolescents. Within each subpopulation, it is imperative to recognize differences because of patient-specific factors (e.g., age, disease, culture) and adapt approaches to suit each individual to provide optimal patient care. The following "checklists" are clinical pearls to keep in mind when caring for patients within each age subpopulation in pediatrics.

Infants and Young Children

- For neonates and premature infants, please refer to the Introduction to Neonatology chapter.
- Educate the caregiver about the purpose, effectiveness, and potential adverse effects of the medication.
- For children younger than 3 years, review birth history and history of illness, including hospitalizations; review medical record for assessment of cognitive and motor skills development.
- Note body weight, height, and head circumference (for infants), and assess growth percentiles (e.g., by using the WHO or CDC growth chart).

- For infants, evaluate weight-based dosing regularly, especially for medications used in chronic illnesses that require dose adjustments with growth (e.g., weight gain).
- Elixir formulations should be avoided because of alcohol content, especially in neonates and young infants, or when chronic use or larger volumes are indicated.
- Be aware of the palatability of medications—if an oral liquid formulation tastes bad, investigate whether an alternative exists in a solid dosage form that is safe to administer as either a crushed tablet or an opened capsule, putting the contents in a palatable vehicle. An example of a poor-tasting oral solution is clindamycin; if a dose fits a capsule size, some clinicians elect opening the capsule in soft food (e.g., applesauce) versus administering the liquid oral formulation.
- Do not crush or modify extended- or sustained-release solid dosage forms.
- Use appropriate measuring devices (e.g., oral syringe) with oral liquid formulations.
- Be aware of potential medication contraindications because of age (e.g., cetriaxone use in premature neonates due to potential to displace bilirubin from albumin and increase risk for kernicterus).
- Often, children around 6 years of age can swallow a tablet or capsule, but this should not be assumed for all children. Ask the patient and caregiver whether liquid or solid dosage forms are preferred.

Older Children and Adolescents

- Educate patients and caregivers about the purpose, effectiveness, and potential adverse effects of the medication.
- Consider issues that are more mature or adult in nature affecting health including alcohol, tobacco, illicit drug use, sexual activity, and psychosocial concerns.
- Adolescence is often considered a "nadir" of medication adherence; thus, education and age-appropriate approaches to improve adherence should be initiated.
- Be aware of the need for increasing independence, including medication administration.
- Involve the patient as an active participant in overall care.

Overall Drug Therapy Assessment

The following are examples of general items that should be considered and assessed as part of selecting, using, and monitoring drug therapy for all pediatric patients (References 2, 3, 5, 7):

- Use correct age, weight (in kilograms), and height.
- Consider social factors such as patient or caregiver health beliefs and culture.
- Correctly use units of measurement such as dose (e.g., milligram vs. gram) and body weight (e.g., kilogram vs. pound).
- Calculate and verify doses by body weight (e.g., actual, ideal, adjusted) as appropriate.
- Evaluate current conditions and determine optimal drug therapy for such conditions.
- Consider comorbidities.
- Evaluate appropriateness of current drug therapy including complementary and alternative medications, supplements, and over-the-counter drugs.
- Assess medication adherence.
- Be careful about inappropriate abbreviations and notations such as trailing zeros (e.g., 1.0 mg) and missing leading zeros (e.g., .1 mg).
- Evaluate for potential adverse drug effects (i.e., ask open-ended questions of patients and/or caregivers).
- Evaluate for drug-drug and drug-food interactions.
- Round doses to measurable amounts. Dose rounding by 10% to the closest measurable dose is common practice. Dose rounding should be avoided in narrow therapeutic index medications (e.g., digoxin).
- Develop a drug therapy monitoring plan with identification and assessment of parameters for efficacy or safety.
- Reconcile medications and dosage regimens at each patient encounter.
- Provide patient and caregiver education. This is not a one-time activity; rather, it should be reinforced at several points of care (e.g., hospital, clinic, pharmacy)—repetition is beneficial!

Patient and Caregiver Education

Patient and caregiver education is fundamental to the care of pediatric patients. Drug therapy can be daunting to some caregivers, especially to new parents or caregivers of patients with a new disease diagnosis. Clinicians should be considerate of their approach when communicating with patients and caregivers including health literacy, culture or beliefs, socioeconomic status, and family structure/dynamic. Information that patients and caregivers should be privy to includes:

- Reason(s) for medication use
- Dose measurement (with appropriate device)
- Medication storage
- Potential adverse drug effects
- Therapy duration

- If therapy is chronic and requires laboratory monitoring, discuss what these tests are, why they are used for monitoring efficacy or safety, and how frequently they would be done.
- Expected therapy outcomes

Educational points should be specific regarding the type of drug therapy to be included in the regimen. For example, specialized information is needed when discussing aerosolized or nebulized medication and use of a nebulizer device. An important educational point in this case is administration technique in the use of a metered dose inhaler with or without a spacer. Other medication administration techniques that patient and caregivers may not be as familiar with are the proper administration of otic drops, ophthalmic drops or ointments, and nasal sprays. Additional information is provided in the Communicating with Children, Adolescents, and Their Caregivers chapter. Patient and caregiver education should be provided in all patient care settings in both inpatient and outpatient environments. Reinforcement of essential points is critical in optimizing medication adherence and safety. Continuity of care should include clear communication between inpatient and outpatient clinic settings. This bridge of care involving health care providers as well as patients and their families is necessary in providing optimal patient care. Pharmacists can bridge the gaps by encouraging patients and their families to ask questions and by providing information about current medications. For example, pharmacists can provide a means for patients and their families to maintain medication lists (written or electronic), thereby empowering them to participate in their health care.

The Present and Future of Pediatric Pharmacy Practice

Pediatric patients are seen in all health care settings, including community pharmacies, clinics, physician offices, community hospitals, and large academic, tertiary institutions. A fundamental understanding of the needs of this special population is essential for the provision of patient care by pharmacists. Although pharmacists in the community setting often lack specialty training in pediatric practice, all pharmacy practitioners should have an appreciation of general concepts in pediatrics, such as approaches to dosing (e.g., milligram per kilogram), unique pharmacokinetics, and drug administration needs, as well as the ability to identify potential drug-related problems (e.g., contraindicated medications for certain age groups).

Pediatric pharmacy practice is a growing specialty area of pharmacy practice, serving future generations of patients with a mission focused on patient advocacy and provision of safe and effective drug therapy through professional responsibility, education, and research. This area of practice will continue to grow with its expansions in the professional pharmacy school curriculum and continued education training in pediatric postgraduate residencies and fellowships. Practice opportunities

Box 1. Examples of general pediatric resources (References 38, 39, 68–73).

Web sites

American Academy of Pediatrics (AAP) – www.aap.org

Pediatric Pharmacy Advocacy Group (PPAG) – www.ppag.org

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**Available in print and electronically.*

in pediatric pharmacy have expanded beyond the pharmacy counter, with an increasing number of pharmacists working as part of interdisciplinary teams in the care of infants, children, and adolescents, from intensive care units to specialist clinics such as cystic fibrosis centers nationwide. Opportunities exist to advance pediatric practice for present and future generations of pharmacists, including expanding the role of pharmacists in areas such as pediatric immunizations, chronic care management, and continuity of care between inpatient and outpatient care. Pharmacists must also initiate and participate in pediatric pharmacotherapy research to advance health care and the profession. Examples of pharmacist-driven innovations include increasing the understanding of approaches to drug therapy management, discovering new therapeutic approaches, and developing behavioral interventions to optimize medication adherence. This partnership of advanced practice and scholarship is what the pharmacy profession must promote to make unique contributions to the body of knowledge in pediatrics and provide quality patient care.

Additional General Pediatric Resources

Additional information regarding pediatric patient care, including medication dosing, extemporaneous compounding, and an overview of general pediatric diseases, can be found in various resources from the Internet to print books (Box 1) (References 38, 39, 68–73). With the growth in information technology, many drug-dosing references are also available by smartphone or tablet computers. Clinicians caring for pediatric patients should have access to at least one pediatric-dosing reference and one reference on general pediatric disease pathophysiology and treatment options.

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CHAPTER 2

Pediatric Pharmacokinetics

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Abbreviations in This Chapter

AAG	α-1-acid glycoprotein
AUC	Area under the curve
CYP	Cytochrome P450
DRP	Digoxin reduction product
GFR	Glomerular filtration rate
GST	Glutathione *S*-transferase
MIC	Minimum inhibitory concentration
P-gp	P-glycoprotein
SULT	Sulfotransferase
UGT	UDP-glucuronosyltransferase
V_d	Volume of distribution

Introduction

The safe and effective use of medications is guided by an understanding of the relationship between dose, exposure, and response. For special populations, including children, much of this knowledge is nonexistent (Reference 1). Despite regulatory initiatives designed to increase the conduct of clinical trials that would enhance our knowledge of pediatric pharmacokinetics, the number of sponsored drug trials conducted in children remains limited (References 2–5). As a result, the drug label tends to offer few data that can be used to guide pediatric pharmacotherapy (Reference 6).

Fortunately, many of the factors that influence dose-exposure relationships are obvious and predictable from recognized patterns of developmental physiology (Reference 7). By contrast, the ontogeny of some physiologic processes is well characterized, but its impact on drug disposition is not readily apparent because of limited historical data that correlate physiology and disposition (i.e., relatively few drugs are susceptible to the biologic process in question). The physiologic factors that drive the disposition of other drugs are not yet defined, and for these drugs, the impact of development will go unappreciated without the conduct of pediatric pharmacokinetic studies (Reference 7).

The sections that follow discuss pediatric drug disposition in the context of existing knowledge on developmental anatomy and physiology. The impact of disease on the disposition of drugs in children is left to other chapters in this textbook. Where human data are lacking, data on the ontogeny of drug disposition pathways in animals are introduced. Attention is drawn to the areas of pediatric pharmacokinetics in which the impact of growth and development remains unknown.

Absorption

Drugs administered by any extravascular route (e.g., oral, sublingual, buccal, intramuscular, percutaneous, rectal) encounter physical, chemical, and mechanical barriers to absorption, irrespective of a patient's age. Of importance, the fundamental mechanisms by which drugs overcome these barriers do not change with age, but the rate and extent to which these processes occur are altered because of normal growth and development.

Peroral Administration

Oral administration is the most common route for drug delivery. Although several chemical and physical factors influence the bioavailability of drugs administered by mouth, one of the most overlooked barriers to oral drug administration resides with the ability to get the drug past the oropharynx. Children will reject medications on the basis of color, taste, texture, and temperature, rendering even the most potent of medicines useless. Taste and smell both play a significant role in the acceptability of oral medications, and clear ontogenic patterns are attributed to gustatory and olfactory development. The ability to perceive sweet tastes appears to be present at birth, with evidence to suggest that the perception of sweet can be detected in utero (e.g., increased fetal swallowing is observed when sweetened solutions are injected into the amniotic sac) (Reference 8). The ability to detect bitter, salty, and sour flavors appears to develop by 2 years of age, whereas the response to trigeminal stimuli (e.g., texture, temperature, piquancy) develops within the first 1–2 years of life. Of note, the affective response to odor does not fully mature until about 5–7 years of age (Reference 8). Consequently, the common formulation strategy of trying to mask an aversive taste with a pleasant odor may not be effective in the young child (Reference 6).

Beyond the oropharynx, several ontogenic processes can influence the bioavailability of orally administered drugs. Children experience a period of relative achlorhydria shortly after birth, despite increased concentrations of circulating gastrin (References 9–11). This failure to

produce adult levels of gastric acid is believed to result from a decrease in receptor responsiveness to gastrin, leading to a higher gastric pH early in life. Discussions of pH are inevitably accompanied by a reference to the Henderson-Hasselbalch equation and the ionized/unionized ratio; however, the stomach is not the primary absorptive site for most orally administered drugs. As such, the consequence of increased pH in the young infant is less applicable to the degree of ionization and more relevant to the chemical stability of the drug being administered. For example, many of the β-lactam and macrolide antibiotics are acid labile, and in adults, a significant fraction of the delivered dose can be broken down before entering the intestine (if an acid-resistant formulation is not employed). By contrast, these same drugs are relatively protected in the stomach of a young infant. As a result, more intact drug will reach the intestine and be available for absorption. Figure 1 illustrates the impact of gastric pH on the absorption profile of penicillin administered at comparable weight-based doses to newborns, infants, and children. As predicted, given our knowledge of developmental gastric physiology, pre- and full-term neonates achieve concentrations 5–6 times higher compared with those observed in infants and children (Reference 12).

For drugs formulated in lipid-based vehicles or lipophilic drugs that require solubilization by bile acids, maturation of biliary function can play a key role in absorption. Postprandial sampling of two major bile salts in the circulation of newborns and young infants reveals that their concentrations exceed those observed in adults. However, the corresponding concentrations within the intestinal lumen are lower through the first 6 months of life. This finding is likely the result of immature bile salt transport into the biliary canaliculus

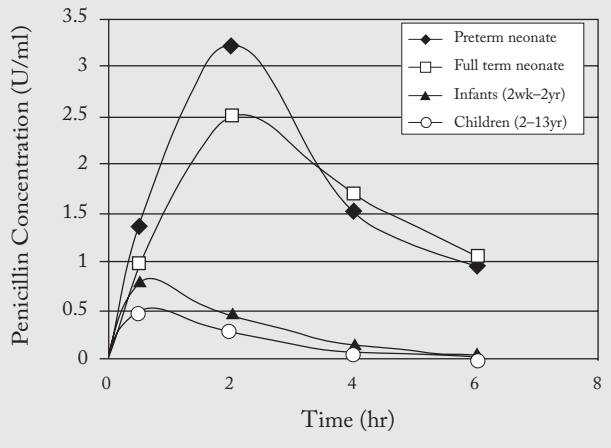


Figure 1. Plasma concentration vs. time profiles for penicillin in neonates, infants, and children after oral administration of a single 10,000-units/lb dose.

(References 13, 14). As a result, the extent of fat absorption is lowest early in the neonatal period (References 15–17). The clinical relevance of this finding can be illustrated by pharmacokinetic studies of the antipicornaviral agent pleconaril, which is formulated in a vehicle of medium-chain triglycerides. Dose escalation in adults shows a proportional increase in total body exposure (Reference 18), whereas a 50% increase in dose delivered to neonates produces no change in either maximum plasma concentration (C_{max}) or area under the curve (AUC) (Reference 19). The capacity-limited absorption observed in the pleconaril studies and in similar studies of a lipid-based chloramphenicol formulation (Reference 20) supports the assertion that knowledge of developmental physiology can guide our understanding of age-dependent changes in dose-exposure relationships. Of note, both intrinsic (i.e., physiology) and extrinsic (i.e., formulation) factors were involved in determining the disposition profiles of these anti-infectives such that the magnitude of their combined influence might not have been predicted without carefully constructed and executed pharmacokinetic studies.

Irrespective of a drug's physiochemical properties, the rate of gastric emptying influences the rate at which the drug is presented to the primary absorptive site (i.e., the small intestine). Gastric-emptying rates increase dramatically during the first week of life (Reference 21); however, several other factors influence this in the newborn period, including prematurity, gastroesophageal reflux disease, respiratory disease, congenital heart disease, and the caloric density of feeds. By extension, intestinal motility also controls the rate at which medications are distributed along the primary absorptive site. The frequency and amplitude of intestinal contractions are reduced in the newborn and young infant, contributing to irregular peristaltic activity shortly after birth (Reference 22). Although highly variable, most children usually attain adult motility patterns by 6–8 months of life (Reference 23). The impact of altered motility on drug absorption will depend, in large part, on the disintegration and dissolution characteristics of the drug molecule and the formulation in which it is administered. The combined effect of both reduced gastric emptying and poorly coordinated intestinal contractility is nicely illustrated by the pharmacokinetic profiles for cisapride. The time to achieve maximal plasma concentrations (T_{max}) averages 5.0 hours in children 28–36 weeks postconception, 4.3 hours in children 36–42 weeks postconception, and 2.2 hours in children 42–54 weeks postconception compared with 1.8 hours in adults (Reference 24).

Even when pharmacologic intervention is employed to enhance gastric emptying and intestinal motility, the maximal attainable absorption rate is limited by age.

Neonates younger than 30 days and infants older than 30 days respond to the prokinetic metoclopramide with an increase in the absorption rate of a concomitantly administered sugar (Figure 2) (Reference 23). However, neonates do not attain the same absolute absorption rate as observed in young infants, suggesting that other developmental factors restrict absorption in the young infant. This has led many pediatric clinicians to attribute reduced absorption rates in young infants to diminished intestinal surface area, yet considered in the context of an infant's primary function (i.e., to assimilate nutrients and grow), a reduction in intestinal surface area would seem counterintuitive. In fact, a careful examination of anatomic and anthropometric data reveals that intestinal villi mature by 20 weeks of gestation and that overall intestinal length, as a percentage of adult values, exceeds other measures including total body length, body weight, and body surface area (Figure 3) (Reference 25). These data refute the assertion of decreased intestinal surface area, leaving no clear explanation for delayed absorption in the young infant. We hypothesize that differences in absorption rate are partially attributed to differences in splanchnic blood flow. Preprandial blood flow velocity increases by 30% to 40% during the first few weeks of life (References 26–28), which may influence the concentration gradient across the intestinal mucosa.

The intestinal lining of the gastrointestinal tract is also an active site of drug biotransformation. Both phase I and phase II enzymes (described in greater detail under Metabolism) are found at varying levels along the gastrointestinal tract. Unfortunately, few studies have examined intestinal enzyme expression as a function of age. Early work examined the activity of several intestinal enzymes from biopsies taken at the duodenojejunal flexure. Among these were epoxide hydrolase, glutathione peroxidase, and aryl hydrocarbon hydroxylase, now referred to as cytochrome P450 (CYP) 1A1 (CYP1A1). Of the three enzymes examined, only CYP1A1 appeared to show some level of developmental dependence, with activity increasing with increasing age (Reference 29). The expression and activity of CYP3A has also been examined in pediatric duodenal biopsies. Neither protein nor activity was detected to any appreciable extent in the fetus; however, a steady increase in both expression and activity was observed from the neonatal period through preadolescence (Reference 30). For orally administered medications that are inactivated by CYP1A1 or CYP3A, reduced presystemic clearance in younger children would be expected.

The phase II enzyme glutathione *S*-transferase (GST) can also be found in the enterocytes of the small intestine. The glutathione-conjugating capacity of distal duodenal biopsies on the antineoplastic busulfan appears to be highest in children younger than 5 years compared with children older than 8 years and adolescents (Reference 31). Of note, the age-dependent activity observed in vitro parallels the changes in the apparent oral clearance of busulfan in vivo, implying that younger children may require higher doses of drugs whose primary route of clearance is by glutathione conjugation. Other phase II enzymes (e.g., UDP-glucuronosyltransferases [UGTs]) are expressed along the intestinal tract at levels comparable to or in excess of those found in the liver; however, no attempts have been made to examine the influence of ontogeny on their expression and/or activity (Reference 32).

We would be remiss not to mention the role of normal intestinal flora on the inactivation (by metabolism) and reactivation (by deconjugation) of orally administered medications, though relevant to only a few drugs.

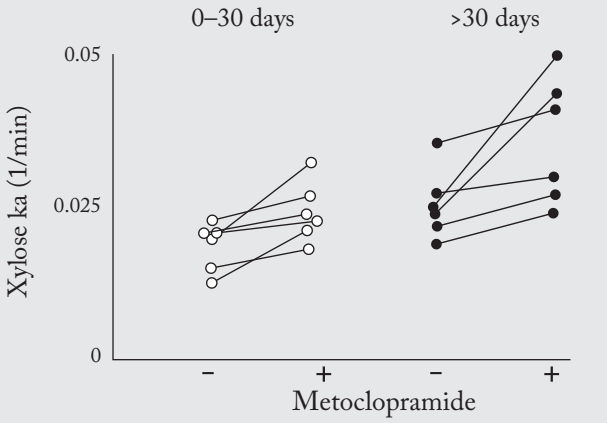


Figure 2. Absorption rate constant of xylose in neonates (younger than 30 days) and young infants (older than 30 days) with and without concurrently administered metoclopramide. Adapted with permission from Reference 23: Heimann G. Enteral absorption and bioavailability in children in relation to age. Eur J Clin Pharmacol 1980;18:43–50.

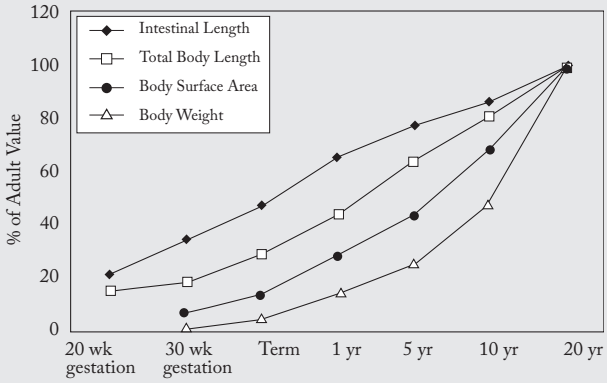


Figure 3. Intestinal length, total body length, body surface area, and body weight with age as a percentage of adult values.

Anaerobic intestinal bacteria that predominate in the intestines of adults mediate digoxin inactivation to digoxin reduction products (DRPs). Recovery of DRPs in the urine of patients receiving digoxin increases steadily from birth through adulthood, with the biggest increase occurring near the time of weaning. This increase in urinary DRPs coincides with an increase in DRP-positive cultures that can be recovered from the stool (Reference 33). Of importance, the predominant bacterial organisms observed in the intestinal tract differ substantially within and between pediatric populations, depending on age and the constitution of feeds (Reference 34). As such, predicting the impact of age on the activity of intestinal microflora is unrealistic.

Finally, intestinal transporters play a considerable role in facilitating or restricting the uptake of many orally administered drugs. Unfortunately, most of the data on the ontogeny of intestinal transporters are from the study of nutrient and ion uptake in animal models. For some transport substrates (e.g., lactose-derived sugars that use the apically situated sodium-glucose cotransporter 1 [SGLT1] and basolaterally situated glucose transporter 2 [GLUT2]), maximal translocation can be observed shortly after birth (Reference 35). For others like iron (absorbed by the divalent metal transporter 1 [DMT1]), the capacity for absorption increases linearly during infancy, attaining adult capacity in early childhood (Figure 4) (References 36, 37). Although limited, data on the ontogeny of drug transporters in children are being acquired directly and indirectly. Studies examining the expression of P-glycoprotein (P-gp) suggest that this transporter is present within the intestine as early as 1 month of age and that it is continuously expressed through adulthood (Reference 38). Other studies allow us to acquire this information indirectly. Pharmacokinetic investigations of the H_2-receptor antagonist nizatidine reveal very little of an age effect when the drug's terminal elimination rate constant is examined. By contrast, apparent oral clearance shows appreciable age-dependent changes, providing support for the developmentally dependent expression of one or more transporters for which the drug may be a substrate (Reference 39). Of note, dietary constituents and phytochemicals can alter the activity of several intestinal transporters, including those found in apple juice (Reference 40). Thus, the potential for drug-nutrient interactions will depend largely on the age-dependent level of expression for the transporters in question.

Extraoral Administration

Although used less commonly as a means of drug delivery, extraoral formulations also encounter developmental barriers that influence the rate and extent to which the drugs they contain enter the body. Rectal administration is an efficient means of drug delivery and is often used in children for whom oral administration is not an option or has proven difficult. However, both formulation and developmental physiology must be considered when employing the rectal route. The number of high-amplitude pulsatile contractions (defined as an amplitude of 80 mm Hg or greater, lasting at least 10 seconds, and propagating at least 30 cm) of the lower gastrointestinal tract is more common in infants than in older children and adults (Reference 41). Although the impact on drug absorption from rectal solutions or fast-melt suppositories may not be significantly affected, suppositories that deliver their contents over hours will very likely be expelled before liberating the entire drug dose.

The impact of altered lower gastrointestinal motility on drug absorption is illustrated by the age-related differences observed in erythromycin concentrations between neonates and children. When administered intravenously, the differences in AUC between neonates, infants, and children are negligible. However, when equivalent weight-based doses are delivered by suppository, bioavailability is markedly lower in neonates (28%) than in infants (36%) and children (54%) (Reference 42). Similarly, acetaminophen delivered rectally at comparable weight-based doses reveals reduced absorption in full-term neonates compared with children and adults. However, preterm neonates show enhanced absorption, likely the result of differences in both motility and metabolism (References 43–45).

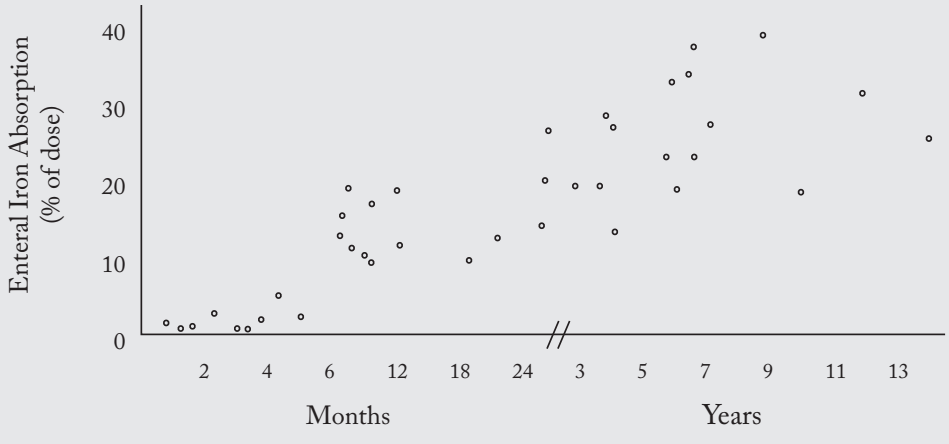


Figure 4. Enteral iron absorption as a percentage of the dose administered. Adapted with permission from Reference 37: Gladtke E, Rind H. Iron therapy during childhood. Ger Med Mon 1966;11:43 8–42.

Percutaneous drug application is rarely exploited for systemic drug delivery in pediatrics. Nonetheless, topical drug administration can be accompanied by significant systemic exposure in children. Children demonstrate a markedly larger surface area per unit of mass than do adults (Figure 3), a greater degree of hydration to their skin (as measured by capacitance, conductance, and transepidermal water loss), and higher rates of perfusion, all of which contribute to enhanced drug permeability (References 46, 47). In addition, premature infants show a thinner stratum corneum than do older children and adults, further facilitating the enhanced translocation of drugs. Although the epidermal and dermal layers can be thinner in full-term newborns and young infants, the primary percutaneous barrier constituted by the uppermost layers of the skin are fully mature in the full-term newborn and even in the preterm newborn by 2 weeks of life (Reference 48). All of these findings, in concert, contribute to an increased risk of systemic toxicity (and, in some cases, death) in infants and children after topical exposure to a variety of chemicals ranging from the therapeutically active (antihistamines, steroids, silver sulfadiazine) to the seemingly inert (talcum powder, laundry detergent) (Reference 49).

Intramuscular absorption represents the final extraoral route of drug delivery that will be reviewed. It is often suggested that absorption after intramuscular administration is erratic in children. For many drugs, however, intramuscular injection can be a very efficient route of drug delivery. Apart from the variability contributed by formulation, capillary density is one of the primary intrinsic drivers of drug absorption when medications are administered by intramuscular injection. Partly because of an increase in metabolic demand, young infants show a 25% increase in skeletal muscle capillary density compared with older children and a 56% increase compared with adults (Reference 50). This increase in capillary density results in greater intramuscular bioavailability for many drugs, including the aminoglycoside and β-lactam antibiotics (Figure 5) (References 51, 52).

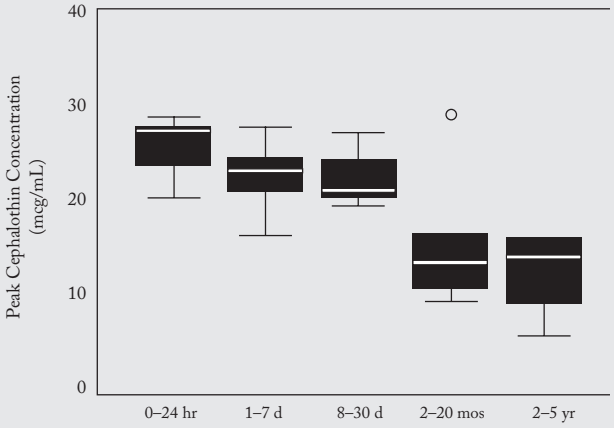


Figure 5. Maximal cephalothin plasma concentrations observed in neonates, infants, and young children after intramuscular administration of a 12.5-mg/kg injection.

Distribution

A drug's volume of distribution (V_d) reflects the size of a compartment necessary to account for the total amount of drug administered, presuming that the drug is present throughout the body at the same concentration as observed in the plasma. Of importance, this theoretical "compartment" does not always correspond to a true physiologic space, and it can be difficult to discern into which tissues a drug distributes without quantitative tissue studies. As a result, the impact of development on drug distribution is not apparent for all drugs; however, this knowledge is available for some drugs that share selected physiochemical characteristics.

At birth, humans exhibit larger fractions of total body water than at any other point in their life. Around 80% of a pre- or full-term newborn's body weight is composed of water, a fraction that gradually decreases throughout the first 4 months of life (Figure 6) (Reference 53). Even the fat stores in these youngest children consist of a higher proportion of water and a lower proportion of lipid compared with the fat of mature adults. Consequently, hydrophilic drugs that restrict their distribution to body water stores show larger apparent distribution volumes and lower plasma concentrations in neonates and young infants.

The clinical impact of expanded body water stores is well illustrated by several classes of antibiotics. The aminoglycosides distribute into a V_d that approximates extracellular fluid. Given their higher extracellular fluid stores, young children experience considerably lower peak gentamicin concentrations after the administration of equivalent weight-based doses. Compared with infants, young children have peak concentrations that are almost 33% greater and almost 50% greater in older children (Reference 54). When their reduced renal clearance is accounted for in the selection of a dosing interval, infants will eventually achieve gentamicin concentrations comparable to those observed in adults. However, the delay can have deleterious clinical consequences for this concentration-dependent drug (References 55, 56). Attaining high peak plasma concentrations early in therapy affords rapid bacterial killing while minimizing the risk of adaptive resistance (References 57, 58).

Linezolid, an oxazolidinone antibiotic, provides a similar example for drugs that distribute into a volume approximating total body water. Based on age-dependent changes in total body water stores, linezolid displays higher V_d values in the neonatal population (0.83 ± 0.18 L/kg) and correspondingly lower maximal plasma

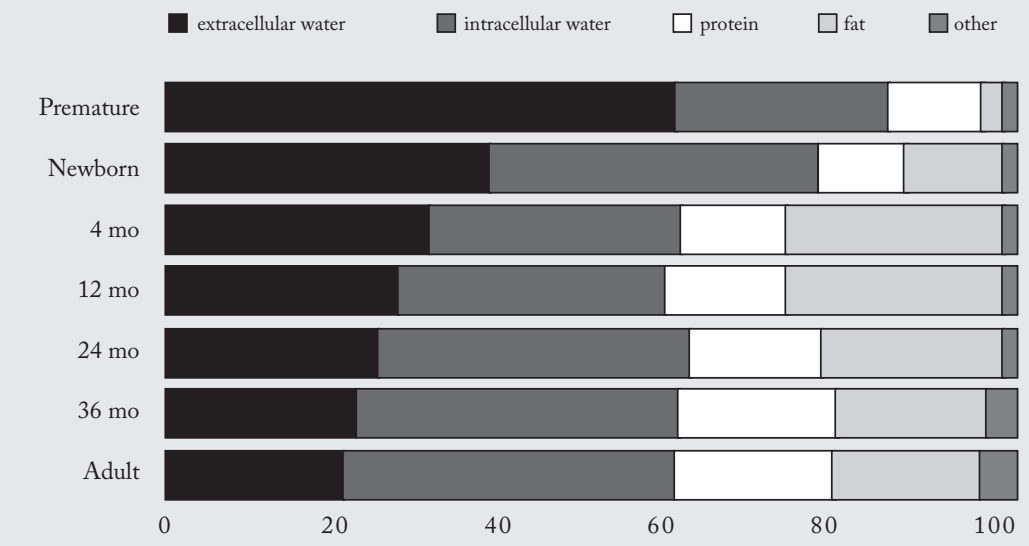


Figure 6. Proportion of body weight accounted for by water, fat, and protein in neonates, infants, young children, and adults.

concentrations (12.5 ± 3.5 mg/L) after a comparable weight-based dose compared with children (0.71 ± 0.18 L/kg, 17.0 ± 5.2 mg/L) and adults (0.63 ± 0.13 L/kg, 19.7 ± 4.9 mg/L). When coupled with the more rapid rate of clearance observed in infants, the clinical implications for this time-dependent antibiotic become apparent. If linezolid were administered with the same weight-adjusted dose and dosing frequency across all age groups, infants would be predicted to spend just 20% to 35% of the dosing interval above the minimum inhibitory concentration (MIC) for susceptible organisms. By comparison, it is predicted that children and adults would spend 35% to 70% and 70% to 100%, respectively, of the dosing interval above the MIC (Reference 59).

In contrast to body water stores, body fat stores are limited in the premature and newborn infant. Considerable increases in body fat stores are seen between 24 and 36 months of life, when the percentage of body fat approaches that of adult values (Figure 6). Although this may seem to suggest that highly lipophilic drugs will exhibit smaller distribution volumes in infants and young children, these drugs, in fact, associate with lipids and other cellular components such that marked distinctions in V_d with age are not as readily apparent.

Another factor that influences drug distribution is the amount of free drug available to translocate from the circulation into peripheral tissue sites. The free fraction of drug is determined, in part, by the binding affinity of the drug for circulating proteins, the concentration of circulating proteins, and the presence of endogenous circulating ligands that have the ability to displace drugs from their protein binding sites (e.g., bilirubin, free fatty acids) (References 60–62). Several physiologic differences in the neonate and young infant predispose them to increases in the free fraction of drugs, among which are the reduction in circulating plasma proteins (e.g., albumin, α-1-acid glycoprotein [AAG]) (Reference 63). In addition, a proportion of the circulating albumin in newborns is constituted by fetal albumin, for which many drugs appear to have a lower binding affinity. Consequently, neonates and young infants (typically younger than 6 months) experience higher unbound fractions of drugs than do older children and adults.

Thiopental, a short-acting barbiturate used primarily for sedation, binds mainly to albumin. Because neonates display higher circulating bilirubin levels and lower albumin stores, they experience a lower percentage of protein binding of thiopental (73.2%) compared with adults (84.4%), resulting in higher free fractions (Reference 64). Sufentanil, a derivative of the opioid analgesic fentanyl, offers a similar example of drugs bound to AAG. Because of reductions in AAG, the free fraction of sufentanil is significantly increased in neonatal (19.5%) and infant (11.5%) populations compared with children (8.1%) and adults (7.8%) (Reference 65).

The clinical impact of developmental differences in protein binding depends in large part on the drug under consideration. For a drug like phenytoin, with its high degree of protein binding and narrow therapeutic index, small changes in protein binding can result in dramatic increases in the drug's free fraction and a corresponding increase in the risk of toxicity. A reduction from 99% protein binding (1% free) to 98% protein binding (2% free) effectively doubles the free fraction of the drug. By contrast, a reduction in ampicillin binding from 22% in adults to 10% in neonates results in a modest (15%) increase in free fraction and a negligible alteration in risk profile (Reference 66).

Finally, growing attention has been paid of late to the many transport proteins that facilitate the vectorial transport of endogenous compounds (e.g., steroids, peptides, nucleotides, electrolytes) as well as a wide range of xenobiotics within the body. The normal biologic substrates of these transporters support somatic development and maintain homeostasis in the growing child. Within different tissues, they are used to different extents at different times throughout development. As such, adaptive mechanisms likely contribute to variability in the tissue-specific expression, quantitative expression, affinity, and turnover rate of transporter proteins during human maturation. Unfortunately, only scant data describe a change in the tissue-specific expression of transport proteins with age. A single study examining P-gp expression in postmortem brain tissue from neonates born between 23 and 42 weeks' gestation suggests that by late gestation, the pattern of P-gp localization is similar to that of adults; however, the quantitative abundance is significantly reduced (Reference 67). By contrast, animal studies have suggested that changes in blood flow and pore density account for differences in central nervous system drug penetration with age; however, the relevance of these findings to humans is unclear.

Metabolism

The human liver is responsible for an array of synthetic, metabolic, and homeostatic functions in addition to its prominent role in the removal of toxins and other foreign substrates from the blood. Although hepatic detoxification pathways likely arose to deal with endogenous ligands and exogenous chemicals or toxins found in nature (e.g., phytochemicals), these pathways serve a dual role as major routes of clearance for an array of medications to which we are exposed. Those classified as phase I enzymes covalently modify drugs (by oxidation, reduction, hydrolysis) to increase their polarity, whereas phase II enzymes act to conjugate endogenously synthesized polar functional groups to the parent drug or any of its phase I metabolites. Of note, several phase I and phase II enzymes are located in tissues other than the liver (e.g., kidney, lung, adipose, intestine, skin); however, these extrahepatic sites (with the exception of the intestine) are of limited quantitative importance, and the discussion that follows will be restricted to the liver.

In the context of interindividual variation in drug metabolism, a review of the literature reveals that far more emphasis is placed on genetic polymorphisms than ontogeny. Scientific investigations that followed the tragedy of chloramphenicol and the "grey baby syndrome" were among the first to reveal the contribution of development to drug biotransformation (Reference 68), and respectable efforts have been made to describe the ontogeny of various hepatic drug metabolism pathways. However, the vast majority of publications focus on the consequence of sequence variations on enzyme activity. Given that genetically encoded variations in the structure or function of drug-metabolizing enzymes remain constant with age, we will not spend time reviewing their significance. However, we would be remiss not to point out the potential relevance (or lack thereof) of polymorphisms in the context of ontogeny. Sequence variations that encode for an enzyme with low or no function have no bearing on the disposition of a substrate if the developmental signal to "turn on" and express the protein has yet to be received. Thus, the ontogenic profiles described below inform more than simply age-dependent changes in the rate and extent of drug biotransformation; they inform whether and to what extent the potential for drug-drug, drug-food, drug-environment, and drug-gene interactions may be experienced.

Phase I Metabolism

The primary drug-metabolizing enzymes responsible for carrying out phase I reactions are the CYPs. The relative contribution of CYPs to medication therapy are the CYP3A family, followed closely by CYP2D6, the CYP2C family, CYP2E1, and finally CYP1A2.

CYP3A4 is estimated to be involved in the metabolism of more than 50% of available medications, including benzodiazepines, calcium channel blockers, and HMG-CoA reductase inhibitors. Humans experience a CYP3A isoform switch shortly after birth, transitioning from the expression of CYP3A7 (responsible for the 16α-hydroxylation of dehydroepiandrosterone) to CYP3A4 (responsible for the 17α-hydroxylation of testosterone). Levels of CYP3A4 increase steadily throughout infancy, maturing to adult levels by 1 year of age (References 69, 70). Consistent with this observation, the clearance of sildenafil, a phosphodiesterase inhibitor metabolized primarily by CYP3A4, rapidly increases within the first 10 days of life, correlating with an increase in the expression of CYP3A4 (Reference 71). Similarly, the terminal half-life of cisapride, a prokinetic agent also primarily metabolized by CYP3A4, is significantly longer in preterm infants younger than 36 weeks' gestational age (11.7 hours) compared with term infants older than 36 weeks' gestational age (7.7 hours), infants older than 42 weeks (4.8 hours), and adults (4.1 hours) (References 24, 72).

The CYP2D6 enzyme is estimated to contribute to the metabolism of 25% of the drugs on the market, including β-blockers, antidepressants, and antipsychotics. The CYP2D6 enzyme is highly polymorphic, with significant interindividual differences observed within and between populations. A study examining CYP2D6

activity from birth through year 1 of life revealed that activity comparable to that of adults can be detected by 2 weeks of age and confirmed that the impact of inheritance on interindividual CYP2D6 variability is of greater significance than development (Reference 73).

Distinct developmental profiles are seen between the two primary isoforms of the CYP2C family. In vitro quantitation of immunoreactive protein from hepatic tissue reveals that CYP2C9 expression appears to be rather invariant with postnatal age, whereas the expression of CYP2C19 appears to increase during the first 6 months of life (Reference 74). Of interest, clinical pharmacokinetic data suggest that the terminal half-life of phenytoin (a primary substrate for CYP2C9) drops from an average of 20 hours at birth to 8 hours by 2 weeks of life (References 75, 76). By contrast, the proton pump inhibitor omeprazole (a substrate for CYP2C19) shows higher rates of clearance in young infants and correspondingly faster half-lives normalizing during the first 5 years of life (References 77–81). Both examples highlight the challenge that can arise when attempting to predict in vivo disposition on the basis of in vitro protein or transcript expression data.

The CYP2E1 enzyme is involved in the metabolism of various anesthetics, including enflurane, halothane, and isoflurane. Transcript, protein, and activity levels are all negligible during prenatal life, with a gradual increase in expression and activity observed throughout childhood. Levels with 80% of adult values are attained after the first year of life (References 82, 83).

The CYP1A2 enzyme metabolizes various substrates, including theophylline, caffeine, clozapine, haloperidol, and duloxetine. Activity levels of CYP1A2 are absent throughout fetal development and extremely low in the neonatal population (4% to 5% of adult levels). A steady increase is observed thereafter, with infants 1–3 months of age showing 10% to 15% of adult levels, infants 3–12 months of age exhibiting 20% to 25% of adult activity, and children 1–9 years of age displaying 50% to 55% of the activity of an adult (Reference 84). Of note, dietary factors can also influence the rate of CYP1A2 metabolism. Examining changes in the disposition of caffeine with age reveals that breast-fed infants are slower to decrease their caffeine half-life compared with infants who are formula fed (References 85, 86).

Phase II Metabolism

Phase II reactions entail the conjugation of drug molecules with endogenously synthesized functional groups (e.g., glucuronic acid, glutathione, glycine, sulfate). These reactions further increase the polarity of intermediate metabolites, making the compound more water-soluble and thereby enhancing its excretion. Several major gene families have been identified that are involved in phase II reactions, including *N*-acetyltransferases (NATs), UGTs, GSTs, and sulfotransferases (SULTs). Analogous to the CYP families, these gene families also have individual isoforms displaying their own ontogenic profile.

The UGTs are among the most well-characterized phase II gene families. UGT1A1 is involved in the metabolism of acetaminophen, ibuprofen, and warfarin among other medications. UGT1A1 activity is shown to be absent in fetal liver, followed by the immediate acquisition of activity shortly after birth and reaching adult levels between 3 and 6 months of life (Reference 87). By contrast, UGT1A9 (substrates include ethinyl estradiol, ibuprofen, and acetaminophen) transcript expression is about 44% that of adult values by 6 months of life and is still only 64% by 2 years of age (Reference 88). UGT2B7, in combination with the UGTs1A, is responsible for the glucuronidation of morphine. Pharmacokinetic data from which morphine clearance is derived suggest that clearance (and by extension UGT2B7 activity) is lowest in premature neonates, increasing exponentially during the first year of life to activity levels that exceed those of adults (Reference 89).

The SULTs play a role in steroid hormone biosynthesis, catecholamine metabolism, and thyroid hormone homeostasis. SULT1A1 is present in the fetal liver, and the levels of expression appear consistent from birth through adolescence. By contrast, SULT2A1 activity levels increase substantially within the first 3 months of life and achieve activity comparable to that of adults after 3 months of age (Reference 90). Finally, both GSTA1 and GSTA2 are present in the prenatal liver; however, adult values are not achieved until 1–2 years of life (Reference 91).

Despite the wide array of developmental profiles observed for the phase I and phase II drug-metabolizing enzymes, neonates and young infants are not always disadvantaged when it comes to clearing xenobiotics. The element of redundancy built into human detoxification pathways means that many drugs undergo biotransformation by multiple enzymes. For some drugs, compensatory mechanisms ensure that the overall clearance rate does not change with age. For other drugs, the contribution of minor pathways, although important, may be less efficient, resulting in delayed drug clearance until maturation of the primary pathway occurs. Acetaminophen offers a great example of the latter scenario. The major routes of metabolism are UGT1A6 and SULT1A1. Sulfate conjugates account for most acetaminophen metabolites recovered in newborns, with a shift in ratio observed with increasing age (Figure 7) (Reference 92). However, infants still exhibit longer overall half-lives than do young children and adolescents (Reference 93). Ultimately, the impact of ontogenic changes in drug metabolism on drug disposition

and action will depend on the nature of the chemical moiety (active drug vs. prodrug), its therapeutic index, and the number of pathways for which the drug serves as a substrate.

Elimination

Although the body uses many organs to facilitate the removal of xenobiotics and endobiotics, the kidneys remain a major organ of elimination for many drugs and/or their metabolites. Both active and passive processes work in concert to clear endogenous and foreign substrates while maintaining normal fluid and electrolyte homeostasis. Of note, the kidney serves as a prototypic organ for which the completion of organogenesis does not signal structural and functional maturation of the organ. Nephrogenesis is complete by 36 weeks' gestation, yet maturation continues through childhood, as reflected by changes in the anatomic dimensions of the organ. Macroscopically, kidney length more than doubles from birth to 12 years of age. Kidney weight exhibits a comparable linear increase during this same time. Microscopically, the diameter of the average glomerulus in a newborn is about 1/3 that of an adult, and the average proximal tubule is about 1/10 the length of that in an adult (Reference 94). The radius of the small pores in the glomerulus increases by more than 25% during the first 3 months of life (from 19.6 to 25 Å), whereas the ratio of large pores to small pores shifts in favor of the former. Neonates also experience an increase in vascular resistance and reduced renal blood flow, with fractional cardiac output to the kidney increasing almost 4-fold during the first year of life (Reference 95).

Because of these and other changes, renal function in children differs quantitatively from that of adults, with both passive and active processes showing clear developmental profiles (Figure 8). Glomerular filtration rate (GFR) increases abruptly after birth, more than doubling in the first 2 weeks of life and increasing uninterrupted until growth is complete. However, when examined with respect to body surface area, adult filtration capacity is achieved in the first 1–2 years of life (References 95, 96). Of note, GFR is significantly decreased in the premature newborn, and postnatal acquisition of functional filtration capacity follows a different trajectory in these children (Figure 9) (Reference 97). Analogous to GFR, concentrating capacity in newborns is significantly diminished at birth, increasing from less than 600 mOsm/kg of water to greater than 900 mOsm/kg of water during the first month of life and ultimately to 1200 mOsm/kg of water when growth is complete (Reference 97).

Based on these observations, gestational and postconceptional age, in addition to comorbid disease processes and coadministered drugs, should be considered

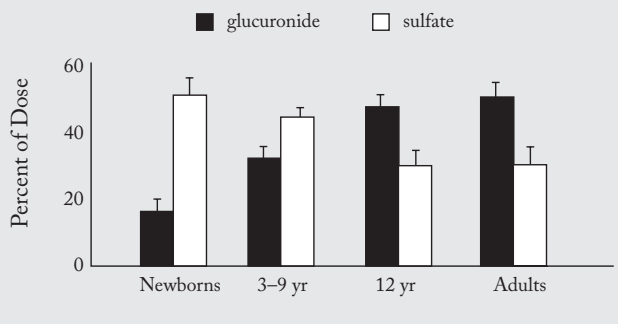


Figure 7. Percentage of an acetaminophen dose recovered as glucuronide or sulfate conjugates in newborns, children, and adults.

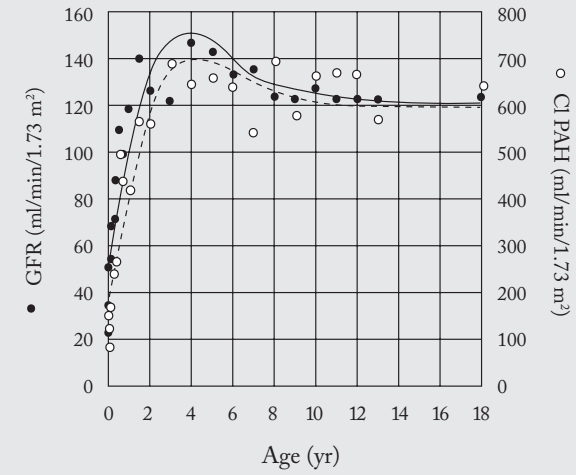


Figure 8. Changes in glomerular filtration (solid circles, solid line) rate and para-aminohippurate clearance (open circles, dashed line) as a function of age.

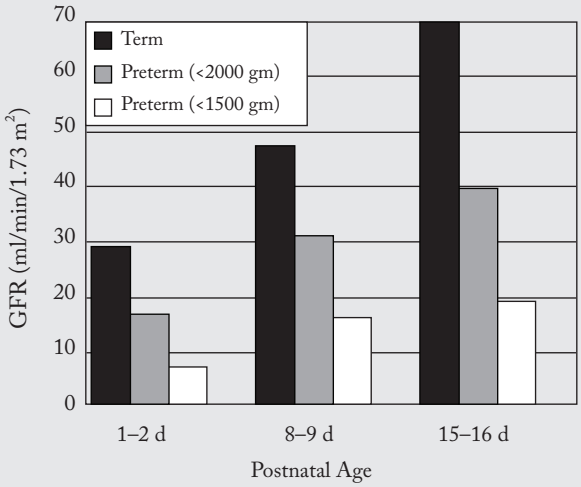


Figure 9. Postnatal acquisition of functional renal filtration capacity as a function of gestational age.

Table 1. Clinically Relevant Renal Drug Transporters

Common Name	Gene	Substrates	Inhibitors
SLC21A3	*OATP-A*	Chlorambucil, fexofenadine, ouabain, rocuronium	Dexamethasone, erythromycin, lovastatin, naloxone, naltrindole, quinidine, verapamil
SLC21A9	*OATP-B*	Benzylpenicillin	
SLC21A11	*OATP-D*	Benzylpenicillin	
SLC21A12	*OATP-E*	Benzylpenicillin	
OCT1	*SLC22A1*	Acyclovir, ganciclovir	Acebutalol, amantadine, cimetidine, clonidine, disopyramide, midazolam, procainamide, prazosin, quinine, quinidine, vecuronium, verapamil
OCT2	*SLC22A2*	Amantadine, memantine	Desipramine, procainamide, quinine
OCT3	*SLC22A3*	Cimetidine	Clonidine, desipramine, imipramine, prazosin, procainamide
OCTN1	*SLC22A4*	Quinidine, verapamil	Cephaloridine, cimetidine, procainamide, quinine
OCTN2	*SLC22A5*	Pyrilamine, quinidine, valproate, verapamil	Cephalosporins, cimetidine, clonidine, desipramine, procainamide, pyrilamine, quinine
OAT1	*SLC22A6*	Methotrexate, acyclovir	ß-Lactam antibiotics, NSAIDs, diuretics
OAT2	*SLC22A7*	Zidovudine	ß-Lactam antibiotics, NSAIDs, diuretics
OAT3	*SLC22A8*	Zidovudine, cimetidine, methotrexate, salicylate	ß-Lactam antibiotics, diuretics, NSAIDs, quinidine
OAT4	*SLC22A11*	Azathioprine, cimetidine, methotrexate	ß-Lactam antibiotics, diuretics, NSAIDs
MRP1	*ABCC1*	Etoposide, methotrexate	Indomethacin, sulfinpyrazone
MRP2	*ABCC2*	Furosemide, indomethacin, methotrexate, vinblastine	Cyclosporin
MRP3	*ABCC3*	Methotrexate	
MRP4	*ABCC4*	Adefovir, azidothymidine, methotrexate	Sildenafil
MRP5	*ABCC5*	Adefovir, 6-mercaptopurine	Sildenafil

ABC = ATP (adenosine triphosphate) binding cassette; MRP = multidrug resistance protein; NSAIDs = nonsteroidal anti-inflammatory drugs; OAT = organic anion transporter; OCT = organic cation transporter; SLC = solute carrier.

when determining age-appropriate pediatric dosage regimens. In young children with decreased renal function, clearance is significantly reduced and the corresponding half-life significantly prolonged, necessitating longer dosing intervals. For example, the half-life of fluconazole in premature infants (88 hours) is considerably longer than in their full-term counterparts (19.5–25 hours). Consequently, fluconazole is dosed as follows. In infants younger than 29 weeks of gestation and younger than 14 days of age, dosing is every 72 hours. In infants younger than 29 weeks of gestation and older than 14 days of age or infants 30–36 weeks of gestation and younger than 14 days of age, dosing is every 48 hours. Finally, in infants 30–36 weeks of gestation and older than 14 days of age, dosing is every 24 hours (Reference 98).

Although age-dependent changes in the clearance of para-aminohippurate (a prototypical substrate for renal transport) have been described, very few data describe the ontogeny of renal drug transporters in the human kidney. However, clear support is available for the assertion of age-dependent changes in the expression of renal transporters. The renal transporters responsible for regulating sodium chloride balance in the body serve to illustrate this point. The apically situated Na^+/H^+ and Cl^-/OH^- transporters, together with the Na^+-K^+-ATPase and chloride transporters located

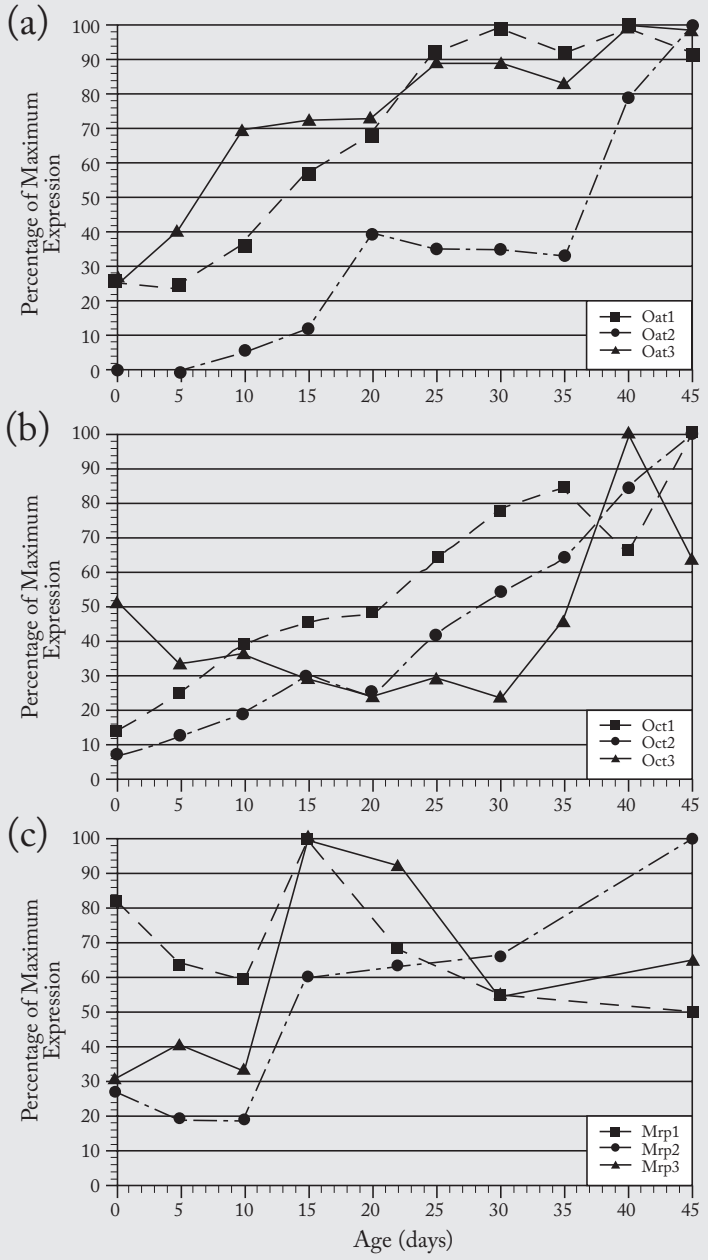


Figure 10. Average transcript expression levels of selected (a) Oat (organic anion transporter), (b) Oct (organic cation transporter), and (c) Mrp (multidrug resistance protein) genes in male and female rodent kidneys.

on the basolateral surface of the tubule, all show diminished activity in fetal and young animals (References 99–102). There is little evidence to implicate the presence of unique transporter isoforms in the young or a difference in the affinity of these transporters for their respective substrates with age. Rather, differences in activity appear to be related to the existence of these transporters in lower abundance along the entire length of the nephron in the young (References 99–101).

Although these renal sodium chloride transporters are not directly involved in drug transport, a substantial number of other proteins situated on both the basolateral and apical surfaces of the tubule take on the task of facilitating diffusion or actively transporting drugs in the kidney (References 103–105). Table 1 highlights the predominant renal transporters that have been characterized to date and offers select examples of drugs that depend on these transporters for their elimination (Reference 103). Because there are no ontogeny data in humans, their known ontogenic profiles in rats (Oat [organic anion transporter], Oct [organic cation transporter]) and mice (Mrp [multidrug resistance protein]) are illustrated in Figure 10 (References 106–110). For reference, the analogous developmental stages between selected animal species and humans are detailed in Table 2 (Reference 111).

An additional, often overlooked route of drug elimination is biliary excretion. Immaturity in the expression of transporters responsible for the translocation of drugs and their metabolites across the biliary canaliculus restricts the biliary clearance of drugs during the first few weeks of life (Reference 112). To compensate, the fractional urinary excretion of many drugs that otherwise rely on biliary transport is increased in the neonate. Around 70% of a ceftriaxone dose is recovered in the urine of neonates compared

Table 2. Analogous Developmental Stages Between Humans and Selected Animal Species

Developmental Stage	Human	Rat	Dog	Pig
Neonate	Birth to 1 mo	Birth to 1 wk	Birth to 3 wk	Birth to 2 wk
Infant	1 mo to 2 yr	1–3 wk	3–6 wk	2–4 wk
Child	2–12 yr	3–9 wk	6 wk to 5 mo	4 wk to 4 mo
Adolescent	12–16 yr	9–13 wk	5 to 9 mo	4–7 mo
Adult	> 16 yr	> 13 wk	> 9 mo	> 7 mo

with children and adults (40% to 60%) (Reference 113). Similarly, the amount of cefoperazone recovered in the urine of preterm newborns (55%) is substantially greater than that of full-term neonates (18%) (Reference 114). Although compensatory clearance pathways exist, the overall rate of clearance for drugs eliminated through the bile will be reduced in the newborn.

Conclusions

To provide optimal care for any special population, clinicians require knowledge of how physiology and pathology intersect to affect the disposition and action of drugs. Children represent a unique "special population" in whom processes involved in normal growth and development overlay the processes that govern disease presentation and progression. Consequently, a fundamental working knowledge of developmental biology is essential for any clinician who chooses to care for children. This knowledge enables the pediatric care provider to make rational recommendations for drug regimen selection when there are limited data in the product label to guide pediatric dosing.

It should be recognized that gaps in our knowledge will be present as long as there are drugs for which the sum total of all disposition processes have yet to be elucidated and known disposition pathways for which the impact of ontogeny has yet to be characterized. In these settings, data generated from carefully constructed clinical pharmacokinetic studies can be used to expand our knowledge of developmental biology. The thoughtful clinician transitioning into pediatric practice should, throughout his or her career, seek to accumulate and assemble both types of knowledge to construct the framework for optimal pediatric pharmacotherapy.

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CHAPTER 3

Introduction to Neonatology

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Learning Objectives

1. Define the human neonate on the basis of gestational and postnatal age.
2. Understand the differences in physiologic development of neonates of varying gestational ages, and differentiate them from older infants and children.
3. Describe the most common disease states associated with premature and full-term neonates.
4. List the most commonly used medications and dosage forms in neonates and methods of administration.
5. Understand the differences in drug dosing and disposition in neonates compared with that in older infants and children.

Abbreviations in This Chapter

ADME	Absorption, distribution, metabolism, and elimination
ELBW	Extremely low birth weight
F_{IO2}	Fraction of inspired oxygen
HBV	Hepatitis B vaccine
ICN	Intensive care nursery
NEC	Necrotizing enterocolitis
NRDS	Neonatal respiratory distress syndrome
PDA	Patent ductus arteriosus
VLBW	Very low birth weight

Introduction

Evolution of the Science of Neonatal-Perinatal Medicine

Historical Perspective

In 1960, Alexander Schaffer coined the term *neonatology* (Reference 1). This term refers to the art and science of diagnosis and treatment of the diseases in the newborn infant. The science of neonatology is quite young, yet it has carved a niche of its own. The term *perinatal* defines the time between the obstetric and neonatal periods. Perinatologists specialize in maternofetal medicine. They take care of pregnant women who are at high risk of pregnancy-related complications. In large academic centers, the perinatal obstetricians and neonatologists work side by side in perinatal centers, giving rise to the specialty of neonatal-perinatal medicine. The first neonatal intensive care nurseries (ICNs) were formed around the early 1900s. Mainly reserved for the premature infant, these ICNs provided "warmth, rest, diet, quiet, sanitation, space" (to use Florence Nightingale's words), and other amenities that prevail today in the modern high-tech ICN and were essential to the growth and survival of the premature neonate.

Connection Between Neonatal ICN vs. Newborn Nursery vs. Home Care of the Newborn Infant

Neonatology bridges obstetrics with pediatrics. Since ancient times, care for pregnant women has relied on midwives, grandmothers, and other experienced female elders. This worked well for uncomplicated pregnancies, but disasters were common in complicated pregnancies, accounting for a significant number of maternal deaths. Specialty care was not provided to the neonate, resulting in high neonatal mortality, especially of premature neonates or those with congenital malformations. Today, the successful care of premature neonates requires a team of health care providers including obstetricians, perinatologists, and neonatologists.

Ethical Dilemmas of Neonatal Practice

The practice of neonatal-perinatal medicine is full of ethical dilemmas, including babies with congenital malformations, extreme prematurity, and birth depression. The lives of these babies can be prolonged by modern technology that provides life support for prolonged durations. However, the long-term neurologic outcome of such births is uncertain. Neonatologists face the ethical dilemma of how much life support to offer and for how long. In some cases, there may be a difference of opinion between the neonatologist and the family. Specialized ethics committees are required in such situations to determine the futility of the situation. Although discussions are ongoing, all health care professionals involved in the care of such infants must provide their full support to the treating physicians, who are ultimately responsible for the infant's outcome.

Epidemiology

During the neonatal-perinatal period, the mother and fetus grow at a fast rate. At birth, the fetus is required to make an abrupt transition from the protective environment of the uterus to the outside. This transition requires the baby to undergo significant physiologic stress. Thus, the highest number of neonatal deaths occur in the first 24 hours of life. Neonatal mortality rate, defined by the World Health Organization (WHO) as the number of deaths during the first 28 completed days of life per 1000 live births in a given year or period, is highest during the first month of life. Newborn, or neonatal, deaths account for 37% of all deaths among children younger than 5 years. The main causes of newborn deaths are prematurity and low birth weight, infections, asphyxia (lack of oxygen at birth), and birth trauma (Figure 1). These causes account for almost 80% of deaths in this age group (Reference 2).

Neonatal deaths may be subdivided into early neonatal deaths, occurring during the first 7 days of life, and late neonatal deaths, occurring after the seventh day but before 28 completed days of life. Perinatal mortality (early neonatal death), defined as the number of stillbirths and deaths in the first week of life per 1000 live births, is a useful additional indicator of maternal and newborn health care and a main component of perinatal mortality reports. Preterm birth is an important perinatal health problem across the globe. Developing countries, especially those in Africa and southern Asia, incur the highest burden in absolute numbers, although a high rate is also observed in North America. In 2005, 12.9 million births, or 9.6% of all births worldwide, were preterm. Around 11 million (85%) of these preterm births were concentrated in Africa and Asia, whereas about 0.5 million occurred in each of Europe and North America and 0.9 million in Latin America and the Caribbean. The highest rates of preterm birth were in Africa and North America (11.9% and 10.6% of all births, respectively), and the lowest rates were in Europe (6.2%) (Reference 3). Figure 2 shows the 2003 infant mortality rate by WHO regions. The infant mortality rate is highest in African nations, which lack access to the modern, technologically advanced ICNs (Reference 2).

The most recent data on infant mortality in the United States come from the National Center for Health Statistics (NCHS), a branch of the Centers for Disease Control and Prevention (CDC).

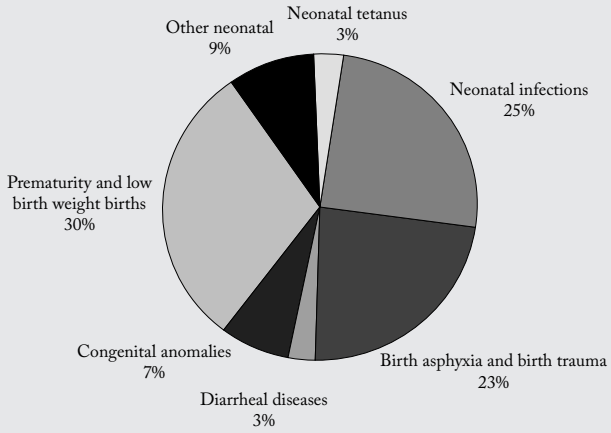


Figure 1. Causes of neonatal deaths.

Source: World Health Organization. The Global Burden of Disease: 2004 update. World Health Organization, Geneva, 2008.

The trends in infant mortality in the United States remained steady between 2000 and 2005. In 2005, the infant mortality rate was 6.86 per 1000 live births (Figure 3). Infant mortality in the United States is highest among non-Hispanic black mothers, as seen in Figure 4. These data were recently published in the National Vital Statistics Report of the NCHS branch of the CDC. Because of their higher risk of death, infants at the low end of gestational age have a large impact on U.S. mortality rates. Figure 5 presents the distribution of live births and infant deaths by gestational age in the United States in 2007; infants younger than 34 weeks account for less than 5% of all infant births but greater than 50% of infant deaths.

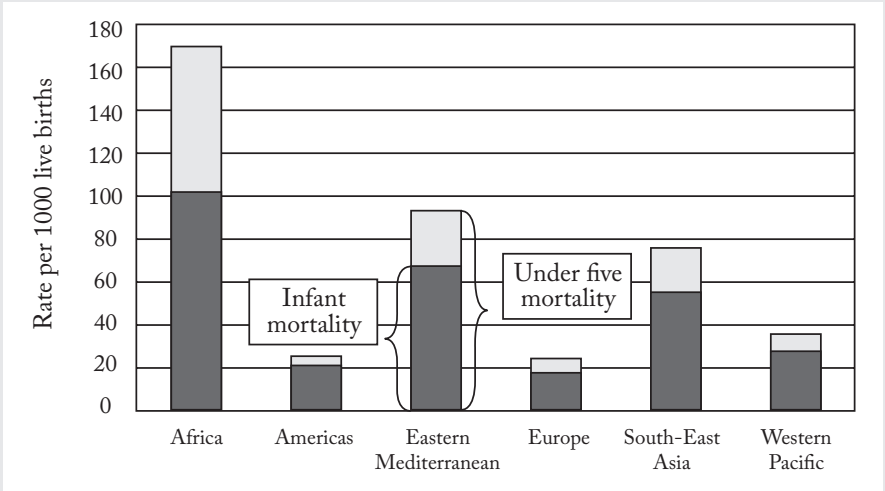


Figure 2. World Health Organization under-five and infant mortality rates, 2003.

Source: Health Status Statistics: Mortality: Under-Five and Infant Mortality Rates. Geneva: WHO Region, 2003. Available at www.who.int/healthinfo/statistics/indneonatalmortality/en/. Accessed May 15, 2012.

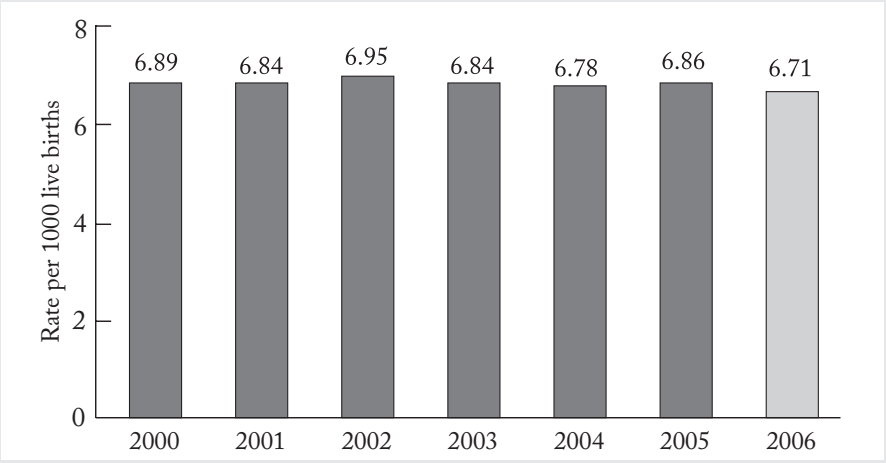


Figure 3. Infant mortality rates in the United States, 2000–2005.

Source: 2000–2005 data are from the linked birth/infant death data sets; 2006 data are from the preliminary mortality file. Available at www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_06.pdf. Accessed May 16, 2012.

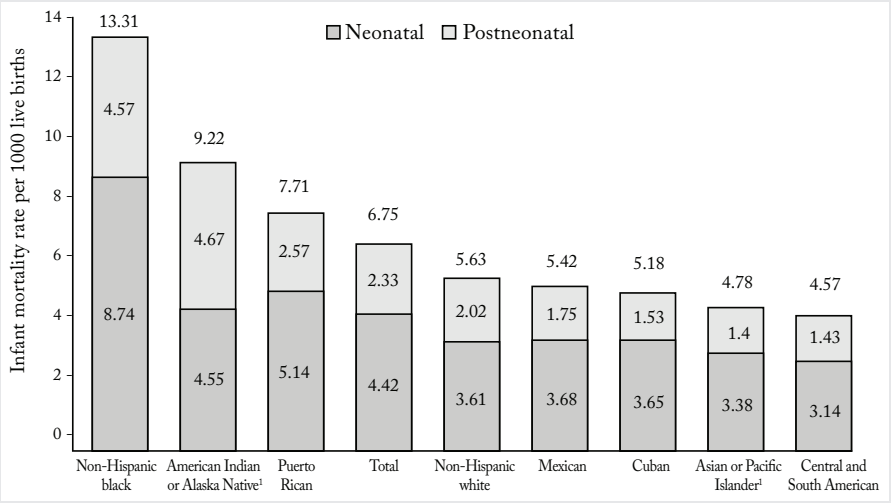


Figure 4. Infant, neonatal, and postneonatal mortality rates by race and Hispanic origin of mothers, United States, 2007.

[1]Includes persons of Hispanic and Non-Hispanic origin. Note: Neonatal is less than 28 days and postneonatal is 28 days to under 1 year. Source: National Vital Statistics System, NCHA, CDC. Available at www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_06.pdf. Accessed May 16, 2012.

How Is the Neonatal Population Different from Other Pediatric Populations?

Defining the Human Neonate

Gestation is defined as the period between conception and birth. In humans, full gestation lasts 37–40 weeks. Infants born before 37 weeks or 259 days of gestation are defined as preterm (or premature) neonates. The neonatal period commences at birth and ends 28 completed days after birth. A neonate is defined as a newborn infant during the first 28 days of life after full gestation. After 28 days, the neonate is referred to as an infant.

Premature neonates may be further divided into subgroups by either gestational age or birth weight. Defining premature infants by gestation is complicated because in many situations the weight and gestational age of the fetus may not correspond because there has been in utero growth retardation from several different causes (e.g., small-for-gestational-age infants who are small because of undernourishment in utero). Likewise, large-for-gestational-age infants weigh much more than anticipated at a given gestation.

The term *low birth weight* defines all infants born with a birth weight less than 2500 g. The term *very low birth weight* (VLBW) refers to infants weighing less than 1500 g, whereas the term *extremely low birth weight* (ELBW) refers to infants weighing less than 1000 g at birth. The care of VLBW and ELBW infants constitutes an important part of all ICNs and is a significant portion of the cost of care (Reference 4). Another term more commonly used in the past 5 years is *late preterm infant*. This term signifies infants born between 34 and 37 weeks' gestation, although there is some controversy surrounding the lower end of gestational age.

Despite these dilemmas, for consistency of care among health care providers in everyday practice, some general definitions are necessary to describe the premature neonates' age after birth. The most commonly used descriptions include postnatal age, corrected gestational age, postmenstrual age, and postconceptional age. Postnatal age refers to the actual chronologic age of the infant after birth. Corrected gestational age, postmenstrual age, and postconceptional age all refer to the same period expressed differently; it is the sum of gestational age and postnatal age.

Multiple Gestations

The incidence of multiple gestations has increased during the past 2 decades, especially in some affluent countries, because of the increased number of pregnancies in older women as well as the increased use of fertility enhancement therapies. The number of births from twin

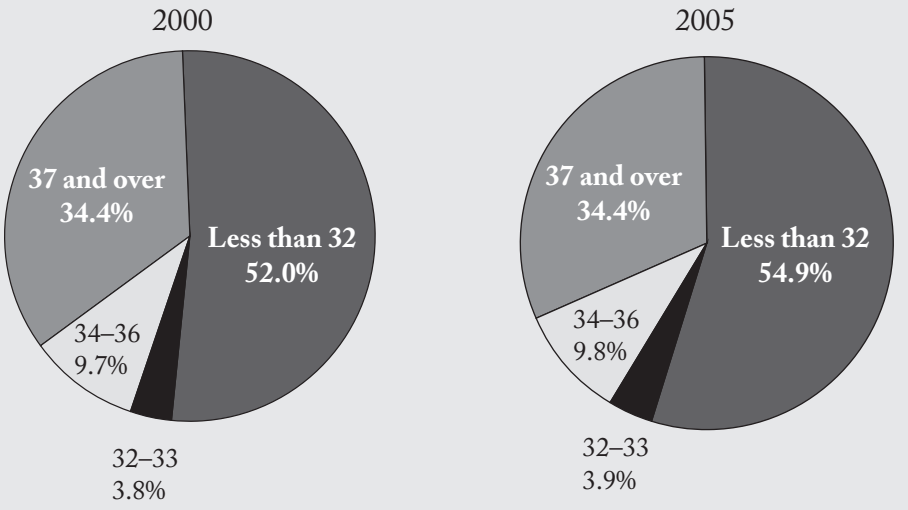


Figure 5. Percentage of infant deaths by weeks of gestation: United States 2000 and 2005.

Available at www.cdc.gov/nchs/data/nvsr/nvsr59/nvsr59_06.pdf. Accessed May 16, 2012.

gestations was about 25 per 1000 live births in the mid-1990s, whereas that from higher-order multiple gestations was around 1.3 per 1000 live births (Reference 5). Fetuses of a multifetal pregnancy are more likely to be born prematurely.

Such pregnancies are also more likely to be complicated by pregnancy-induced hypertension, premature onset of labor, and antenatal and postpartum hemorrhages, among other complications.

Developmental Differences—Ontogeny of Organs and Organ Function

The development and function of organs in an infant are a matter of gestational age and postnatal age. In a full-term neonate, the organs in the body are mature for age at the time of birth. In a premature neonate, birth has occurred before the internal organs of the body are fully developed. However, compared with infants and children, premature and full-term neonates are both still considered to have immature organ function.

The ontogeny of organs affects the absorption, distribution, metabolism, and excretion (ADME) of drugs (Reference 6). Developmental changes in surface area of the skin, gastrointestinal tract, and other mucosal surfaces such as the rectum and oral cavity can affect the rate and extent of drug absorption significantly in the neonatal period. Changes in body composition occur with increasing age. About 70% to 80% of a neonate's body weight is water. This affects the distribution of drugs significantly, resulting in larger volumes of distribution for water-soluble drugs in neonates compared with infants, older children, and adolescents. Conversely, lipid-soluble drugs do not distribute extensively in water, and they may be needed in lower doses. The plasma binding proteins such as albumin and α-1-acid glycoprotein are present in lower concentrations, especially in premature infants, resulting in much higher plasma concentrations of free or pharmacologically active drugs.

Hepatic metabolism of drugs is also limited and varies according to gestational age, especially in the premature neonate. Phase I oxidative metabolism and phase II reactions such as glucuronidation are slow in the premature neonate and mature only around 6 months of age.

The functional and anatomic maturation of the kidneys is a dynamic process in the neonate beginning around 9 weeks' gestation and continuing well into early childhood. The glomerular filtration rate increases rapidly in the first 2 weeks of life in the term neonate. In the premature infant, this maturation is slower, thus affecting the clearance of compounds exclusively eliminated by the kidney. Dosage adjustments for drugs eliminated exclusively by the renal route are essential when renal function is compromised because of age, underlying illness, or both. (See the Introduction to Pediatrics and the Pediatric Pharmacokinetics chapters for more details.)

Fundamentals in the Care of the Neonate

Maternal Obstetric, Labor, and Delivery History

A mother may be exposed to many prescribed and unprescribed substances during the course of pregnancy as well as during labor and delivery that may adversely affect the neonate. In caring for the neonate, a detailed history of in utero drug or other substance exposure is critical because such substances may transfer to the infant through the placenta and affect the initial treatment of the newborn infant.

Placental Transfer of Drugs and Other Substances

In utero, the fetus relies on the placenta (the fetus is connected to the placenta by the umbilical cord) almost completely for nutritional, respiratory, and excretory functions. The placenta grows in parallel with the fetus. During pregnancy, substances may cross the placenta by simple diffusion, facilitated diffusion (gradient-dependent diffusion), active transport (transfer requires specific transporters that use energy to transfer substances, mostly for lipid-insoluble substances), receptor-mediated endocytosis, and other mechanisms.

Most drugs travel across the placenta by active transport or passive diffusion. Exposure of the mother to anesthetic or analgesic agents, tocolytic agents, and nicotine, cocaine, or other substances of abuse can have adverse effects on the neonate. Knowledge of such history before the delivery of the neonate can help the care provider be prepared for successful resuscitation of the neonate.

Neonate-Specific Considerations

Neonatal Resuscitation

The transition from fetal to extrauterine life is a complex process that requires understanding of in utero physiology and potential complications that may occur during the process of labor and delivery. Most full-term and low-birth-weight infants transition from intrauterine to extrauterine life with little or no assistance. They are vigorous and cry at birth, breathing easily afterward. The remaining may require varying degrees of resuscitation for restoring cardiopulmonary function to allow adjustment to extrauterine life.

Normal Physiologic Events at Birth

In utero, the fetal lungs are filled with fluid, providing an area of high resistance. The oxygenation of the blood occurs in the placenta. This circulation is maintained by two main patent fetal shunts—the foramen ovale and ductus arteriosus. These shunts provide connections to the right atrium and aorta, respectively, shunting the blood away from the pulmonary circulation. Relatively little blood reaches the lungs because of high pulmonary vascular resistance.

Clamping of umbilical vessels removes the low-resistance placental circulation and raises the systemic blood pressure. The pulmonary vascular resistance decreases with lung expansion and increased oxygenation, resulting in increased pulmonary blood flow (Figure 6). As a result, the pulmonary venous return and left atrial pressure increase. In full-term infants, this results in closure of the two fetal shunts, thus creating normal systemic circulation. This process takes about 24–48 hours. Anatomic closure follows in about 8–10 days, causing permanent closure of the shunts.

Abnormal Physiologic Events at Birth

If the lungs fail to expand after birth and spontaneous respiration is not established, the result is residual lung fluid, hypoxemia and acidosis, and hypercapnia caused by inefficient breathing and pulmonary vasoconstriction, leading to reduced pulmonary blood flow. The systemic vascular resistance does not increase. The fetal shunts remain open and continue to shunt blood. The direction of the shunting is dependent on the resistance present in the lungs and the systemic circulation. In such situations, complications arise, leading to the use of mechanical ventilation and blood pressure medications to support the systemic blood pressure.

An abnormal physiologic transition sometimes requires significant resuscitative measures in the neonate, including cardiopulmonary resuscitation with bag-mask ventilation, chest compressions, and use of medications such as epinephrine when indicated. The course of events that follows abnormal physiologic transition at birth can result in different types of complications in the premature and full-term infant. Some of these complications are discussed briefly later in this chapter.

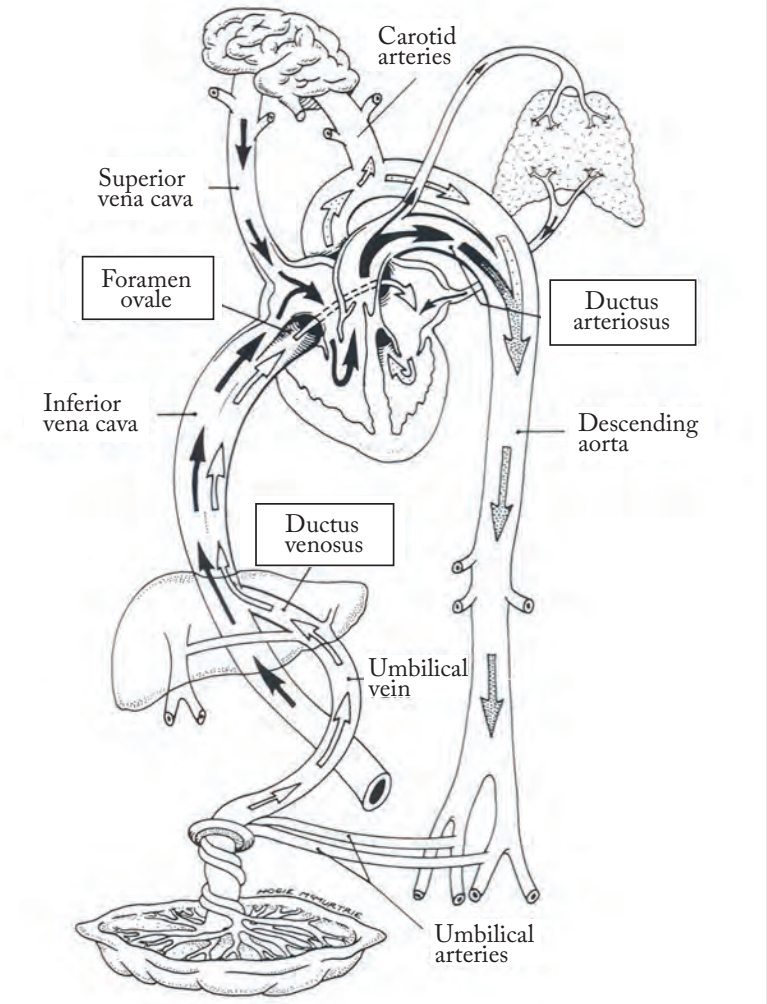


Figure 6. Fetal circulation.

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Initial Stabilization and Assessment

When an infant is born, the first step in the stabilization process is thermoregulation. Newborn infants have immature thermoregulatory systems and lack adequate body fat. The large surface area-to-body mass ratio is susceptible to cold stress. Both of these factors predispose the neonate to hypothermia. This is especially important in a term or preterm neonate who is hypoxic at birth. Hypoxia blunts the normal response to cold and can make the neonate hypothermic. Hypo- and hyperthermia both can lead to adverse neurologic consequences. It is therefore essential to gain control of body temperature as soon as possible. To prevent excessive heat loss from the body caused by external environmental factors, the neonate must be received in a warm blanket and dried immediately. The full-term neonate acquires the ability to maintain adequate body temperature soon after birth. In some cases, however, the neonate may need to be placed under a radiant warmer for 24–48 hours to maintain normal body temperature. Premature infants are initially placed under radiant warmers and then transitioned to thermoregulated incubators as soon as possible after stabilization. They stay in the controlled-temperature environment until they have acquired an adequate surface area-to-body mass ratio, typically around 2000 g of body weight.

APGAR Scores

Initial assessment of a newborn infant during the resuscitative phase includes assessment of appearance and vital signs, APGAR scores (Table 1) (Reference 7), gestational age assessment, and measurement of weight, length, and head circumference as well as a complete physical examination to identify any congenital anomalies. The weight, length, and head circumference measurements are plotted on corresponding sex-appropriate growth charts available for infants from birth to 36 months of age. The growth charts for full-term infants are easily available and reliable. The neonate's initial weight, length, and head circumference are plotted on the day of birth, and the growth thereafter is followed through 36 months of life to determine whether it is normal. See the Introduction to Pediatrics chapter for examples of growth charts. There are separate charts for boys and girls. More charts can be viewed at the following Web site: www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdf (Reference 8). Separate charts exist for premature infants beginning at 22 weeks' gestation. These charts allow a comparison of an infant's growth, first with the fetus as early as 22 weeks and then with the term infant to 10 weeks' corrected gestational age (Reference 9).

Gestational Age Assessment

The best estimate of gestational age is antenatal ultrasonography. If the infant's gestational age is uncertain, it can be determined to within around 2 weeks using a standardized scoring system such as the Ballard scoring method (Reference 10). The New Ballard Score is a set of procedures developed by Jeanne L. Ballard, M.D., to determine gestational age through the neuromuscular and physical assessment of a newborn infant, including the extremely premature newborn infant. The method uses score sheets for neuromuscular and physical maturity and assigns scores for each. The gestational age is derived from these scores.

Caring for the Full-term Neonate

Full-term Healthy Neonate

A normal nursery can provide routine care for healthy, full-term newborn infants born at 37 weeks or more gestation. Neonates born at 35 weeks' gestation weighing at least 2000 g and otherwise healthy may also be cared for in a normal nursery. Close monitoring for respiratory distress, poor color, diaphoresis, jitteriness, or abnormal tone should occur for the first 6–12 hours of life.

Table 1. APGAR Scoring System[a]

Sign	0	1	2
Heart rate	Absent	< 100 beats/minute	> 100 beats/minute
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Flaccid	Some flexion of extremities	Active motion
Reflex irritability	No response	Grimace	Vigorous cry
Color	Pale	Cyanotic	Completely (whole body) pink

[a]In practice, patients are scored at 1 and 5 minutes of life. Maximum score = 10; minimum score = 0.
Adapted with permission from Apgar V. A proposal for a new method of evaluation of the newborn infant. Curr Res Anesth Analg 1953;32:260–7.

Feedings

These neonates should be offered feeding by mouth. Breast milk is the preferred nutrition for a newborn infant. Breastfeeding is initiated shortly after birth once the neonate shows signs of hunger. However, at times, breast milk must be avoided because of maternal intake of prescription drugs that may cross into breast milk and adversely affect the neonate. If breast milk is unavailable or the mother chooses not to breastfeed, an iron-fortified cow milk–based infant formula should be used. Most term infants will take 15–30 mL every 3–4 hours in the first 1–3 days of life and about 75–90 mL by day 5 of life.

Vitamin K

The American Academy of Pediatrics recommends that every neonate receive a single intramuscular dose of 0.5–1 mg of vitamin K (phytonadione) within 1 hour of birth to prevent vitamin K–dependent hemorrhagic disease of the newborn. This is a neonatal condition caused by vitamin K deficiency, the combined result of a lack of unbound maternal vitamin K, immaturity of the fetal liver, and lack of vitamin K–producing bacteria in the infant colon. Clinically, the condition may arise abruptly in the early postpartum period with spontaneous nasogastric or intracranial hemorrhage. The condition affects up to 1 in 1000 neonates and carries 5% to 30% mortality, if untreated. The condition may be more common in breastfed infants and is more severe and of earlier onset in infants of mothers receiving anticonvulsives. Breastfed infants are at higher risk of developing hemorrhagic disease because of low concentrations of vitamin K in breast milk together with colonization of bacteria in the gut that are unable to produce vitamin K. Vitamin K does not cross the placental wall, resulting in low stores in the newborn infant.

Eye Prophylaxis

All newborn infants should receive an application of a 1- or 2-cm ribbon of sterile erythromycin (0.5%) eye ointment for prophylaxis against gonococcal ophthalmia neonatorum, ensuring that the treatment reaches all parts of the conjunctival sac.

Newborn Screening

Each state has developed guidelines for newborn screening. This is a preventive public health strategy used for early identification of treatable disorders that significantly affect health and development. The disorders screened vary from state to state depending on the prevalence of the disorders in each state. Some of the more commonly screened disorders may include disorders of amino acid metabolism, fatty acid oxidation disorders, organic acid disorders, endocrine disorders such as congenital hypothyroidism and congenital adrenal hypoplasia, hemoglobinopathies such as β-thalassemia, cystic fibrosis, and galactosemia and biotinidase deficiencies. Screening for these disorders has had a significant impact on the morbidity and mortality from metabolic disorders.

Physiologic Neonatal Jaundice

Neonatal physiologic jaundice (also referred to as indirect hyperbilirubinemia) is a condition in which the level of unconjugated bilirubin is increased because of the infant's inability to rapidly clear it from the body. It can occur in both premature and full-term infants. Jaundice, usually seen first in the face, progresses to the trunk and extremities. Because high bilirubin levels stain the skin and sclera of the eye yellow, the condition is often first recognized by parents who bring the yellow staining to the attention of the health care providers. Two-thirds of all newborn infants will appear jaundiced during the first few days of life. In most cases in which the infant is feeding well, this condition will resolve itself without intervention. Breastfed full-term newborn infants have higher bilirubin levels than formula-fed infants. Frequent breastfeeding every 2–3 hours helps resolve this problem.

When feeding cannot be established well in the first few days of life, which is most often the case in premature infants but can also occur in full-term infants, hyperbilirubinemia may become a pathologic issue needing intervention. If intervention is needed, the American Academy of Pediatrics guidelines for evaluation and treatment of jaundice should be followed (Reference 11). Untreated indirect hyperbilirubinemia can have severe neurologic consequences. Acute bilirubin encephalopathy can cause lethargy, hypotonia, and poor suck. In advanced stages, irreversible neurologic damage can occur and may sometimes lead to coma and death if left untreated for a prolonged time.

Immunizations

All neonates (premature, low birth weight, and full term) born to mothers who are positive for hepatitis B surface antigen must routinely receive hepatitis B immunoglobulin (HBIG) (0.5 mL intramuscularly) and hepatitis B vaccine (HBV) (0.5 mL intramuscularly) within 12 hours of life. This prevents or significantly reduces the vertical transmission of the disease in infants born to mothers with a positive test for hepatitis B surface antigen. If HBV cannot be administered to a full-term infant together with or soon after HBIG, it should be administered within the first 7 days of life. For premature infants or sick low-birth-weight infants in whom the vaccine cannot be given within the prescribed period with HBIG, it must be given within the first month of life or at the earliest opportunity when the infant is clinically able to tolerate the

vaccine. All infants born to hepatitis B surface antigen–positive mothers should receive additional HBV at 1, 2–3, and 6–7 months of chronologic age for four doses total. Full-term neonates born to hepatitis B surface antigen–negative mothers should receive the vaccine by 2 months of age. For preterm infants weighing less than 2 kg born to hepatitis B surface active antigen–negative mothers, the optimal time to initiate the first dose of HBV is at 30 days' chronologic age if medically stable or at hospital discharge if stabilization occurs before 30 days of age (Reference 12). (For further details, please refer to the Pediatric Vaccines chapter.)

Full-term Sick Neonates

Many full-term neonates are at risk of developing perinatally acquired infections. Neonatal sepsis in full-term newborn infants is rare, but it can be potentially life threatening. Risk factors for acquiring such infections include prolonged rupture of fetal membranes, maternal chorioamnionitis, maternal colonization with group B *Streptococcus*, prematurity, and maternal urinary tract infection. Thus, the most common organisms found in the perinatal period include group B *Streptococcus* and *Escherichia coli*. These sick full-term neonates require cardiorespiratory support and intensive nursing care. Such neonates are admitted to the neonatal ICN, where they are assessed for sepsis. Other common diseases found in such infants that may require ICN admission and close observation include transient tachypnea of the newborn period, meconium aspiration syndrome, neonatal seizure, neonatal hypoxic-ischemic encephalopathy, acute hypoglycemia in infants of diabetic mothers, and congenital surgical or cardiac conditions.

These neonates are cared for in the ICN until the underlying illness has resolved or been surgically treated and the infant is fully recovered, able to maintain temperature without assistance, and able to breathe on its own, with well-established nutrition to meet nutritional needs for growth and development.

Selected Common Diseases of the Full-term Neonate

Infants of Diabetic Mothers

Diabetes mellitus is a common medical complication of pregnancy affecting 2%–3% of all pregnancies. Infants of diabetic mothers are generally large for gestational age or macrosomic. They are at risk of developing cardiomegaly, hyperbilirubinemia, and polycythemia, and they may have congenital malformations. Good control of maternal glucose concentrations during pregnancy is important for the well-being of the fetus. Because of the increased glucose demand by the growing fetus, the plasma glucose concentrations in normal and diabetic pregnancies are lower than in the immediate postpartum period. For women who develop gestational diabetes, as well as for those who were diabetic before becoming pregnant, maintaining tight glucose control and glucose concentrations near normal values for adults is essential.

These infants may develop acute hypoglycemia (blood glucose less than 35 mg/dL in full-term infants and less than 25 mg/dL in premature infants) in the immediate postnatal period. Low glucose concentrations may cause lethargy, hypotonia, seizures, poor feeding, apnea, or jitters. Metabolic derangements such as hypocalcemia and hypomagnesemia are also common.

Fluids and electrolytes are the mainstay of treatment. Acute hypoglycemia should be treated with an initial bolus dose of glucose 10% (2–5 mL/kg), and early, frequent oral feeding should be instituted. Intravenous continuous glucose infusion, with electrolytes if needed, should be initiated to deliver an initial glucose load of 7–8 mg/kg/minute. This can gradually be weaned as oral feedings are established. Frequent blood glucose concentration checks are needed until a stable oral nutritional regimen is established that maintains blood glucose in the normal range (40–60 mg/dL). Symptomatic treatment of respiratory distress is essential.

Meconium Aspiration

Meconium is the earliest stools of an infant. It is composed of materials ingested while the infant is in the uterus and consists of intestinal epithelial cells, lanugo, mucus, amniotic fluid, bile, and water. Meconium is almost sterile, viscous, and sticky like tar, with no odor. It should be completely passed by the end of the first few days of life, with the stools progressing toward yellow (digested milk). The presence of meconium in the amniotic fluid suggests an in utero asphyxia episode. Aspiration of this meconium can lead to significant morbidity and mortality if left untreated. The passage and aspiration of meconium are not seen in neonates younger than 34 weeks' gestation. At delivery, if the amniotic fluid is meconium stained, then aggressive suctioning of the meconium at the perineum is indicated. After the neonate is delivered, the oropharynx should be suctioned below the vocal cords to ensure that the meconium is not aspirated into the lungs. Meconium aspiration can lead to chemical pneumonitis and respiratory distress, with severe cases requiring mechanical ventilator support. Supportive measures may include the use of vasopressors for maintaining blood pressure, intravenous fluids, and sedatives and analgesics to keep the neonate compliant with mechanical ventilation. In severe cases, pulmonary hypertension may develop. Inhaled nitric oxide is often used as a pulmonary vasodilator in such cases.

Caring for the Premature Neonate

Premature infants are born at younger than 37 weeks' gestation. The shorter the pregnancy, the greater the risks of mortality and morbidity. Organ development corresponds directly to gestational age. The earliest gestational age at which the infant has at least a 50% chance of survival is generally believed to be 24 weeks, although rare exceptions exist. Surviving premature neonates are at risk of short- and long-term complications of gastrointestinal issues (necrotizing enterocolitis [NEC]), respiratory issues (respiratory distress syndrome and chronic lung disease), neurologic issues (apnea of prematurity, hypoxic-ischemic encephalopathy, retinopathy of prematurity, cerebral palsy, and developmental delay), cardiovascular issues (patent ductus arteriosus [PDA]), and hematologic issues (pathologic jaundice). In addition, premature neonates are at higher risk of infectious complications (sepsis and pneumonia).

In developed countries, all premature neonates are cared for in ICNs. Modern ICNs allow continuous cardiorespiratory monitoring, administration of intravenous fluids and nutrition, mechanical ventilator support, and administration of a variety of intravenous medications. However, premature infants cared for in an ICN are also at greater risk of nosocomial infections, which contribute to the morbidity and mortality of these patients.

Selected Common Diseases and Complications of the Premature Neonate

Apnea of Prematurity

Premature neonates have an immature respiratory pattern because of an underdeveloped brain stem. Periodic breathing (short recurring pauses in respiration lasting 5–10 seconds) is common in prematurity and considered the normal respiratory pattern at that age. A respiratory pause that is prolonged (more than 20 seconds) with complete cessation of breathing or one that is associated with cyanosis and/or bradycardia is defined as apnea of prematurity. The problem increases in severity and frequency with decreasing gestational age. The causes of apnea with or without bradycardia and desaturation may be multifactorial and may include thermal instability, metabolic disorders (electrolyte abnormalities and hypoglycemia), central nervous system disorders (intraventricular hemorrhage, seizures, and encephalopathies), infection, decreased oxygen delivery to the brain (secondary to PDA, hypotension, shock), or airway obstruction (from an ill-positioned neck or a mechanical obstruction of the oropharynx), all of which should be ruled out when apneic episodes begin. Once other causes are ruled out, the diagnosis of true idiopathic apnea of prematurity is confirmed.

Treatment includes nonpharmacologic and pharmacologic measures. Nonpharmacologic measures include tactile stimulation, increasing fraction of inspired oxygen (FIO_2), and use of respiratory support such as continuous positive airway pressure or mechanical ventilation.

Pharmacologic measures primarily include the use of methylxanthines, caffeine and theophylline, which theoretically increase the sensitivity of the chemoreceptors in the brain to carbon dioxide, although this mechanism has not been proved in the human neonate (Reference 13). Apnea of prematurity is generally resolved at greater than 34 weeks' corrected gestational age. At this time, all neonates should be challenged to breathe without the help of methylxanthines, and treatment should be weaned off, preferably before discharge (Reference 14). Further details about apnea of prematurity management are available in the Apnea of Prematurity chapter.

Necrotizing Enterocolitis

Necrotizing enterocolitis is among the most common gastrointestinal problems in the premature neonate. It is characterized by partial- or full-thickness intestinal ischemia. Although the terminal ileum is usually involved, NEC can occur in any part of the intestine. The exact cause of NEC is unknown, but factors leading to intestinal ischemia are implicated. Reperfusion injury after acute ischemia to the intestines has been proposed as a mechanism for injury. The most commonly known risk factors include prematurity, formula feeding (especially hyperosmolar formulas), neonatal stress, infection, and surgery in the newborn period. Feeding precedes NEC symptomatology in most NEC cases. It is unclear whether the volume or rate of feeding plays a major role in the pathogenesis of NEC. Overall, NEC appears to be a multifactorial disorder that requires a delicate balance between intestinal perfusion, intestinal flora, and type of enteral nutrition.

The clinical features of NEC are nonspecific. Temperature instability, lethargy, feeding intolerance, and abdominal distension are generally the first signs. Blood may be present in the stools. Apnea, bilious vomiting, and signs of shock may develop with advanced disease possibly caused by infection from enteric bacteria. An abdominal radiograph in NEC is characteristic with pneumatosis intestinalis (free air in the peritoneum) and portal venous gas in advanced disease.

Treatment includes bowel rest, nasogastric suction, intravenous fluids (including parenteral nutrition), and broad-spectrum antibiotics for about 2 weeks. Medications to support blood pressure may be necessary. Intestinal perforation warrants surgical intervention. Occasionally, portions of the intestine may become necrosed and require surgical removal. These infants have

permanent short bowel. Long-term complications of NEC include the formation of strictures in the affected part of the intestine and difficulty with feeding, especially in short bowel syndrome (Reference 15).

Neonatal Respiratory Distress Syndrome

Neonatal respiratory distress syndrome (NRDS) is a condition produced by surfactant deficiency in the lungs. It is present to some extent in all premature infants born younger than 34 weeks' gestation. The extent of deficiency is inversely proportional to gestational age. The surfactant is a substance consisting of phospholipids and proteins that is naturally produced by the body. Its function is to produce surface tension at the interface of the alveoli and the air in the lungs and keep the alveoli open so that adequate gas exchange may occur. Neonatal respiratory distress syndrome is most common in VLBW and ELBW infants, although it does occur in low-birth-weight infants. The ELBW infants are intubated for mechanical ventilator support within minutes of birth. These infants may not exhibit the typical clinical course of NRDS.

Early signs and symptoms of surfactant deficiency include difficulty in initiating normal respirations, expiratory grunting, sternal and intercostal retractions, nasal flaring, cyanosis on room air, and tachypnea. Chest radiography shows a reticulogranular, ground-glass pattern with air bronchograms, which is characteristic of NRDS. Physiologically, there is reduced lung compliance, ventilation perfusion mismatch caused by decreased alveolar ventilation resulting in hypoxemia, and hypercarbia with metabolic acidosis if the hypoxemia is severe.

Treatment of NRDS consists primarily of surfactant replacement therapy and mechanical ventilator support. Premature infants may be administered surfactant as soon as the diagnosis of NRDS is confirmed by radiologic examination and intubation has been performed. In ELBW infants, it may be beneficial to administer prophylactic surfactant as soon as possible after intubation. Surfactant administration results in improved lung compliance with improved oxygenation and lower F_{IO_2} requirements. Improved compliance allows effective ventilation at lower peak inspiratory pressures, thus reducing the potential for lung injury. Complications of surfactant treatment, such as oxygen desaturation and bradycardia, are common secondary to airway occlusion during surfactant administration. A rapid change in lung compliance may result in hyperventilation and overdistension, potentially increasing the risk of pneumothorax.

Several surfactant products are commercially available. These and other options for treating neonatal respiratory distress syndrome are described in detail in the Neonatal Respiratory Distress Syndrome and Bronchopulmonary Dysplasia chapter (Reference 16).

Patent Ductus Arteriosus

Patent ductus arteriosus (Figure 6) is an essential shunt in utero. Once the fetus is delivered, successful transition from fetal to neonatal circulation is essential and occurs naturally in full-term neonates. Patent ductus arteriosus results when such transitions are incomplete or do not occur. The incidence of PDA is inversely related to gestational age. An untreated PDA can result in significant morbidity and mortality. Congestive heart failure and hypoperfusion of the brain (increased potential for intraventricular hemorrhage), kidneys (acute tubular necrosis), and intestine (potential for NEC) secondary to PDA can cause increased morbidity.

Clinical diagnosis of a PDA is made when a systolic murmur is detected together with a hyperdynamic precordium, bounding palmer pulses, increased pulse pressure, and signs of congestive heart failure (tachypnea, tachycardia, edema, and hepatomegaly). Occasionally, refractory hypotension or pulmonary hemorrhage is also seen. Chest radiography reveals pulmonary edema and an enlarged heart. Definitive diagnosis is made by an echocardiogram that shows a PDA with a left-to-right shunt detected by Doppler studies.

Treatment of PDA is warranted in neonates who are symptomatic from it. Management of PDA falls into three categories: medical, pharmacologic, and surgical. Medical management includes use of fluid restriction and diuretics to manage congestive heart failure and allow the PDA time to close physiologically. This approach is sometimes successful, with some PDAs closing permanently, whereas others close transiently and reopen, requiring a more definitive intervention. Fluid restriction severely restricts the caloric intake of an infant. Electrolyte abnormalities and need for higher mechanical ventilator settings are common with this approach.

Pharmacologic management includes the use of drugs that cause ductal closure. The ductus arteriosus is sensitive to prostaglandins. While in utero, its patency is maintained by the high levels of circulating prostaglandins produced by the placenta. The arterial oxygen concentration, which is low in utero, also plays a role in keeping the ductus open. Once the neonate is separated from the placenta, prostaglandin concentrations are decreased and oxygenation is established, increasing oxygen concentrations in the blood. Both of these factors aid in ductal closure. Although this process occurs as part of normal adaptation in the full-term infant, in premature neonates the circulating prostaglandin levels remain high after birth, allowing the ductus to remain open in the postnatal period.

Nonsteroidal inflammatory agents are useful in the treatment of PDA by inhibiting prostaglandin production. Both intravenous ibuprofen and indomethacin are effective in ductal closure. Intravenous ibuprofen has some advantages over indomethacin such as

reduced adverse effect on renal function compared with the severe oliguria often seen with intravenous indomethacin (Reference 17). Surgical ligation is indicated when pharmacologic treatment has failed or when it is contraindicated.

Other Common Conditions in Full-term and Premature Neonates

Neonatal Sepsis

Around 1–5 of 1000 newborn infants are afflicted with sepsis. The incidence increases to 40–50 in 1000 in infants weighing less than 2500 g, with further increase as birth weight decreases (References 18, 19). Neonatal sepsis at any stage carries significant morbidity and mortality. Surviving infants may sustain significant neurodevelopmental sequelae.

The pathogens responsible during early sepsis (younger than 5 days of life) are those vertically transmitted at birth. Group B *Streptococcus* and coliforms (*E. coli*) are the most common organisms colonizing the birth canal. Clinical signs and symptoms of neonatal sepsis are nonspecific and may include temperature instability, hypotension, frequent oxygen desaturations, apnea, increased work of breathing, and poor weight gain. Early sepsis is suspected in infants of mothers with chorioamnionitis, ill infants of mothers with unknown group B streptococcal status, prematurity when there is no obvious explanation for premature delivery, and prolonged rupture of membranes (generally 18–24 hours before birth).

Late-onset infections are generally those that occur after the first 5 days of life. The most common pathogens suspected in late-onset sepsis may be community acquired (*Streptococcus pneumoniae*, *Haemophilus influenza,* or late-onset group B streptococcal infections) or hospital ICN acquired (coagulase-negative and coagulase-positive staphylococci, *E. coli*, *Enterococcus* spp., and *Klebsiella* spp.). Clinical signs and symptoms of late-onset sepsis are also nonspecific and may include manifestations such as lethargy, poor feeding, apnea, jaundice, cyanosis, hypotension, metabolic acidosis, and respiratory distress. Common risk factors include prolonged instrumentation such as the presence of indwelling central or peripheral catheters for intravenous access, endotracheal tubes for mechanical ventilation, repetitive or prolonged courses of antibiotics, and other nosocomial risk factors such as human handling of ELBW infants.

Prompt diagnosis of early- and late-onset infections and initiation of early empiric treatment until microbiologic results are returned are essential. Once the microbiologic results are known, therapy can be tailored on the basis of institution-specific susceptibility results. Doses and duration of selected antibiotic regimens should consider efficacy, toxicity, and appropriate coverage of suspected organisms and the site of infection. A detailed discussion of the treatment of neonatal infections is available in the Neonatal Sepsis chapter.

Seizure Disorders

In pre- and full-term infants, seizures can be caused by a wide variety of underlying conditions. Repetitive seizures are associated with increased morbidity and mortality and require prompt treatment. Neonatal seizures are relatively common and rarely idiopathic. In most cases, they are of consequence if there is an underlying cause that should be sought and treated. Neonatal seizures are clinically distinct from those in older infants and children. They are generally more difficult to diagnose clinically and may require electroencephalogram (EEG) monitoring. Neonatal jitteriness is sometimes confused with seizures. The two entities can be distinguished by the effectiveness of applying mild pressure to the body, which will stop jitteriness but not seizures. More than 50% of neonatal seizures occur on the first day of life (Reference 20). Risk factors include hypoxic-ischemic encephalopathy, electrolyte abnormalities, hyperbilirubinemia, inborn errors of metabolism, drug toxicity (including in utero exposure immediately before delivery, which should be suspected if seizures occur within a few hours of birth), drug withdrawal, and idiopathic neonatal seizures. Seizures in neonates can be subtle, focal, or generalized.

Diagnosis is made on the basis of the results obtained in a complete workup for metabolic derangements, labor and delivery history, toxicology screening to identify in utero drug exposure, and imaging studies of the brain, including a video EEG if warranted.

Treatment of neonatal seizures involves treating the underlying cause, if one is identified, as well as the seizures themselves. Etiology-specific therapy is critical because it may prevent further brain injury. This is particularly true for the seizures associated with some metabolic disorders (e.g., hypoglycemia, hypocalcemia, and hypomagnesemia) and with central nervous system or systemic infections. Furthermore, neonatal seizures may not be effectively controlled with antiepileptic drugs unless their underlying cause is treated. Pharmacologic management of the seizures themselves is aimed at halting seizure activity. Intravenous phenobarbital and phenytoin are used as first-line agents (Reference 21). Benzodiazepines may be used for immediate control of status epilepticus. Appropriate monitoring of plasma concentrations of drugs as well as adverse effects is essential. Other supportive measures such as vasopressors for hemodynamic support and mechanical ventilation for respiratory support may be necessary.

Considerations for Medication Administration in the Neonate

Neonates in the ICN pose unique challenges to the system for prescribing, dispensing, administering, and monitoring medications, primarily because of the lack of available well-researched data on how to use medications effectively in this population (Reference 22). Issues of drug administration in the neonate can be categorized into three groups: ADME, choice of administration route, and dosage preparation and drug compatibility. Physiologic differences between children and adults are well recognized. In pre- and full-term neonates, these differences are enhanced a step further. In fact, the physiologic differences between pre- and full-term neonates are significant enough to warrant dosing modifications. Nevertheless, little is known about the ADME of many drugs used in this population. One must often use one's knowledge of the physiologic basis of drug effectiveness and the dosage form at hand to determine a safe and effective dose and route of drug administration in a neonate. (See the Pediatric Pharmacokinetics chapter.) The second issue is safe drug administration. Although many different administration routes are possible for many drugs, in neonates, there is a limitation on the use of these formulations because of insufficient absorption of the active compound by oral, rectal, or intramuscular routes. Most drugs in critically ill neonates are administered intravenously.

Intravenous Access and Medication Administration (References 23, 24)

Intravenous drug administration requires the infant to have an intravenous catheter placed for drug administration. The catheter may be placed in a large vein (central venous catheter) or in a small peripheral vein. The insertion site has implications in drug administration because drugs with a high osmolar load may cause vein irritation if administered by the peripheral vein route. Decisions regarding drug concentrations and acceptable osmolarities must be made with knowledge regarding catheter placement. Most intravenous drugs used in neonates will require further dilution before administration to measure accurately. The dispensing pharmacists must provide a chemically stable, appropriately diluted solution that may be safely administered without the risk of vein irritation and fluid overload in the infant, who may have fluid restrictions merely because of size.

Intravenous access is often very limited in neonates. Once the drug is received at the bedside, a determination must be made about its compatibility with other solutions running through the intravenous catheter. Incompatibilities can result in precipitation of the drug in the catheter, and infused precipitate can act as a nidus for clot formation in the vein, leading to compromised blood flow. Smart pumps are routinely used in ICNs for drug administration. Although these infusion pumps are designed for safe drug administration, errors in pump setting can lead to medication administration errors. A streamlined medication use process from prescribing to drug administration is necessary for the safe and effective administration of medications in the ICN (Reference 25).

Drug Dosing in Neonates

Drug dosing in neonates is generally based on weight. Factors such as organ maturation may also be considered. Thus, neonatal dosing recommendations may be given on the basis of weight as well as postnatal age or postconceptional age. The ADME of a drug may vary depending on gestational age and/or postnatal age. There are few dosing guidelines available for commonly used drugs in the neonate. Neonatal pharmacy practitioners must be aware of the current literature and use their knowledge of pharmacokinetics and pharmacodynamics to determine a safe dose. Neonates will lose about 10% of their body weight in the first week of life. Thus, it is appropriate to use birth weight as dosing weight during this time. Once the neonate has regained birth weight, subsequent dosing may be based on actual weight. However, this may not always be possible in critically ill neonates who may have increased total body weight because of water retention and body edema. In such cases, an estimate of dry weight corresponding to the infant's gestational and postnatal age may be obtained from standardized growth charts available from sources such as the CDC.

Vital Sign and Laboratory Assessment

Temperature

It is unusual for neonates to develop fever except in response to environmental factors. Rectal temperature is less likely to be affected by environmental changes unless the changes are prolonged; rectal temperature is thus a better measure than skin temperature. A sustained rectal temperature of more than 38°C (100.4°F) requires further evaluation of the neonate for infectious or neurologic issues. Premature infants often become hypothermic in response to environmental temperature fluctuations. Prolonged hypothermia also requires further evaluation.

Respiratory and Heart Rate

The respiratory rate in a full-term neonate is measured by counting chest movements for a full minute. The normal rate in a full-term healthy neonate is 30–60 inspirations per minute. Premature neonates may have respiratory rates at the upper end of normal range.

The heart rate in healthy full-term infants is generally 110–160 beats/minute. Premature neonates have resting heart rates at the upper end of normal range. Heart rate may vary significantly in sick full-term and premature neonates. Tachycardia, defined as a heart rate persistently greater than 160 beats/minute, warrants further investigation. In preterm infants, a heart rate persistently less than 90 beats/minute constitutes bradycardia that requires further investigation.

Blood Pressure

Blood pressure varies widely at different gestational ages. At least three separate measurements are needed before diagnosing hypertension in a neonate. The range of normal blood pressures in the neonate depends on the method of measurement (invasive vs. noninvasive measurements) as well as gestational age. In general, the mean arterial pressures provide a better estimate of blood pressure than systolic or diastolic blood pressure alone because it considers both the systolic and diastolic blood pressure (mean arterial pressure = [(2x diastolic) + systolic]/3). The average systolic, diastolic, and mean blood pressure during the first 12 hours of life in normal newborn infants grouped according to birth weight have been described (Reference 26). Sick newborn infants may experience significant blood pressure fluctuations and may deviate substantially from the normal blood pressures shown in this reference.

Hypotension is more common in critically ill infants. The treatment threshold for hypotension varies significantly depending on whether the hypotension is compromising systemic perfusion measured by clinical indicators such as capillary refill, skin color, and urine output. Thus, the perfusion status of an individual infant is a far better determinant of the significance of hypotension.

Laboratory Values

There are no neonate-specific reference ranges of laboratory values for commonly used tests such as blood chemistries, hematology tests, or liver function tests. These values in neonates are generally compared with those in older children or adults. The serum creatinine in the first 48 hours of life is not a reliable indicator of kidney function in the neonate because it often reflects the mother's serum creatinine. In the full-term infant, the values reflect true renal function in about 48 hours after feedings or intravenous hydration is established.

The reference ranges used also do not differ for pre- and full-term neonates. However, ELBW infants pose a particular challenge in maintaining a normal electrolyte balance because of their inability to conserve sodium and bicarbonate given their immature kidney function. These infants often have metabolic acidosis and hypernatremia during the first few days of life. In premature infants, it is difficult to predict when renal function will become normal because renal dysfunction may be a consequence of prematurity as well as underlying illness. In the neonatal period, it is often more useful to follow trends in laboratory values rather than single values to assess the fluid and electrolyte status and organ function.

Future of Neonatal Pharmacy Practice

Neonatal pharmacy practice requires skilled personnel with a clear understanding of the impact of the ontogeny of organ function on the ADME and the pathogenesis of neonatal disease states. Appropriately experienced and trained neonatal clinical pharmacy practitioners are vital to the safe and effective treatment of diseases in a very special subpopulation at high risk of adverse events. Despite advances in diagnostic technology and newer technologically advanced methods of drug preparation and administration, this population remains vulnerable to medication errors. Drug dosing in neonates continues to remain a challenge after more than 50 years of the inception of this science and continues to test the knowledge and skills of the neonatal practitioner, who must make clinical judgments on the basis of knowledge of the disease states, pharmaceutical dosage forms, and existing drug dosage information in older populations. The need for such skills is now recognized by pediatric health care professionals outside the pharmacy profession (Reference 27). Neonatal clinical pharmacy practitioners of the future will require advanced training and experience in domains such as epidemiology, pathophysiology, and pharmacotherapeutics of neonatal diseases, as well as in-depth knowledge of pharmacokinetics, pharmacodynamics, and pharmacogenomics. They will also need to understand the impact of interplay of these processes on drug disposition and issues in neonatal medication safety, as well as gain expertise in neonatal translational research, to contribute to the current gaps in knowledge of neonatal pharmacotherapeutics.

Conclusions

Neonatal-perinatal medicine and neonatal pharmacotherapeutics have progressed significantly since the inception of these sciences in the twentieth century. Challenges of the twenty-first century are highlighted in hope that the advances in understanding of neonatal disease states at the molecular level will allow more targeted drug therapy and advances in neonatal pharmacotherapeutics.

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CHAPTER 4

Medication Safety

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Learning Objectives

1. Provide a background for the basis of medication safety as a national public health initiative.
2. Explain unique differences specific to pediatric patients that make them more vulnerable to adverse events.
3. Describe specific medication error preventive strategies and important considerations for pediatric patients.
4. Describe the role of automation and technology in medication safety.

Abbreviations in This Chapter

ADE	Adverse drug event
ASHP	American Society of Health-System Pharmacists
BCMA	Barcode medication administration
CDSS	Clinical decision support systems
CPOE	Computerized prescriber order entry
IOM	Institute of Medicine
ISMP	Institute for Safe Medication Practices
PPAG	Pediatric Pharmacy Advocacy Group
TJC	The Joint Commission

Introduction

Medical errors are common and costly, and they may result in significant harm or injury (Reference 1). More than a decade ago, the Institute of Medicine (IOM) published its initial report *To Err Is Human*, which served as the catalyst for health care reform and patient safety. The IOM estimated that 44,000–98,000 people experience a medical error annually, making medical errors the eighth leading cause of death, with a multibillion dollar price tag. These alarming statistics provided the necessary leverage to make creating a safer health care system part of the national agenda and a public health concern (Reference 1). In 2001, the IOM released a follow-up report titled *Crossing the Quality Chasm*, which provided the blueprint for health care redesign with a focus on health care technology (Reference 2).

Overall, progress has been made to improve patient safety; however, complete reform of health care has not been achieved (Reference 2). The IOM's most recent progress report, titled *Preventing Medication Errors*, served as a more comprehensive analysis of quality and safety and provided the framework to advance the health care industry to a higher standard (Reference 3). The IOM summarized several recommendations as part of this health care improvement plan, including patient-focused care, medication management standards, implementation of technology, and improved communication among health care providers. The IOM also recommended more funding for medication safety research and additional oversight by regulatory organizations to provide incentives for institutions that have implemented best practices in the safe use of medications. Pharmacy-specific recommendations included monitoring of medication adverse events, patient education and discharge teaching, medication reconciliation, use of electronic prescribing, minimizing alerts from clinical decision support tools, and surveillance of patients at risk of adverse events.

Medications are estimated to harm at least 1.5 million people annually (Reference 3). Pediatric patients are at highest risk because of several unique differences characteristic of this patient population. This chapter provides the foundation for a basic understanding of medication safety and a summary of key preventive strategies, with a focus on pediatric-specific considerations.

Definitions

The National Coordinating Council for Medication Error Reporting Program (NCC MERP) defines a medication error as

> any preventable event that may cause or lead to inappropriate medication use or patient harm, whereas the drug is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and medication use systems including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use. (Reference 4)

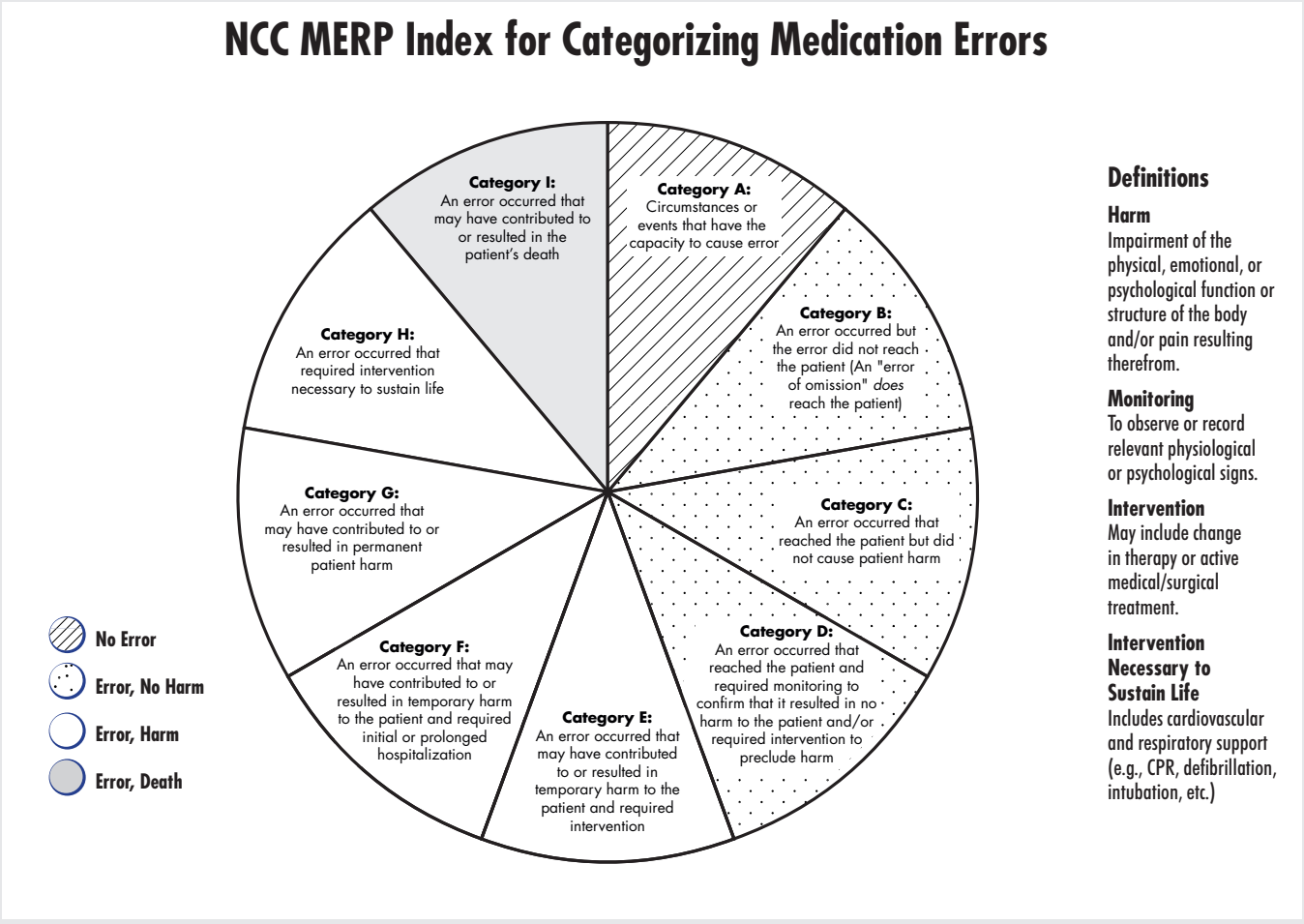


Figure 1. National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Index for Categorizing Medication Errors (Reference 5).

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The NCC MERP categorizes medication errors on the basis of severity, as shown in Figure 1. Medication errors may or may not result in harm to the patient. An adverse drug event (ADE) occurs as a result of harm caused by the use of a drug. Potential ADEs are events that could result in harm but did not harm the patient. Not all ADEs are the result of a medication error, but all medication errors have the potential to result in an ADE (Reference 6). When a medication error is intercepted before the medication is administered to the patient, it is referred to as a "near miss". Near misses can provide an opportunity for systems to be reviewed for error-prone steps which allows institutions to be proactive instead of reactive to errors. Specific medication error types and common causes for medication errors are summarized in Table 1 and Box 1.

Adverse drug reactions (ADRs) are defined as unintended, undesired, or excessive responses to therapy that are typically unpreventable and may be associated with a medication dosed normally over time or with a single dose. Adverse effects of a medication are not ADRs because they are expected and based on known drug properties. ADRs are the unexpected harmful effects of a drug when used appropriately. Pharmacists are responsible for monitoring and reporting ADRs as part of an organized mediation safety program (References 6, 8).

Incidence/Frequency

In 1984, the Harvard Medical Practice Study estimated that 3.7% of hospitalized patients experience an adverse event related to medication therapy. Of these, about 70% were preventable; 30% of patients experienced significant morbidity and mortality as a result (References 9–11). The Adverse Drug Event Prevention Study sought to further describe medication errors and ADEs. This study found that medication-related ADEs occurred commonly in adults at a rate of 6.5 per 100 patient admissions, and most were preventable. In

Table 1. Types of Medication Errors[a] (Reference 7)

Type	Definition
Prescribing error	Incorrect drug selection (based on indications, contraindications, known allergies, existing drug therapy, and other factors), dose, dosage form, quantity, route, concentration, rate of administration, or instructions for use of a drug product ordered or authorized by physician (or other legitimate prescriber), illegible prescriptions, or medication orders that lead to errors that reach the patient
Omission error[b]	The failure to administer an ordered dose to a patient before the next scheduled dose, if any
Wrong time error	Administration of medication outside a predefined time interval from its scheduled administration time (this interval should be established by each individual health care facility)
Unauthorized drug error[c]	Administration to the patient of medication not authorized by a legitimate prescriber for the patient
Improper dose error[d]	Administration to the patient of a dose that is greater or less than the amount ordered by the prescriber or administration of duplicate doses to the patient (i.e., one or more dosage units in addition to those that were ordered)
Wrong dosage-form error[e]	Administration to the patient of a drug product in a different dosage form than ordered by the prescriber
Wrong drug-preparation error[f]	Drug product incorrectly formulated or manipulated before administration
Wrong administration-technique error[g]	Inappropriate procedure or improper technique in the administration of a drug
Deteriorated drug error[h]	Administration of a drug that has expired or for which the physical or chemical dosage-form integrity has been compromised
Monitoring error	Failure to review a prescribed regimen for appropriateness and detection of problems, or failure to use appropriate clinical and laboratory data for adequate assessment of patient response to prescribed therapy
Compliance error	Inappropriate patient behavior regarding adherence to a prescribed medication regimen
Other medication error	Any medication error that does not fall into one of the above predefined categories

[a]The categories may not be mutually exclusive because of the multidisciplinary and multifactorial nature of medication errors.
[b]Assumes no prescribing error. Excluded would be (1) a patient's refusal to take the medication or (2) a decision not to administer the dose because of recognized contraindications. If an explanation for the omission is apparent (e.g., patient was away from nursing unit for tests or medication was unavailable), that reason is documented in the appropriate records.
[c]This would include, for example, wrong drug, a dose given to the wrong patient, unordered drugs, and doses given outside a stated set of clinical guidelines or protocols.
[d]Excluded would be (1) allowable deviations based on preset ranges established by individual health care organizations in consideration of measuring devices routinely provided to those who administer drugs to patients (e.g., not administering a dose based on a patient's measured temperature or blood glucose level) or other factors such as conversion of doses expressed in the apothecary system to the metric system and (2) topical dosage forms for which medication orders are not expressed quantitatively.
[e]Excluded would be accepted protocols (established by the Pharmacy & Therapeutics Committee or its equivalent) that authorize pharmacists to dispense alternative dosage forms for patients with special needs (e.g., liquid formulations for patients with nasogastric tubes or those who have difficulty swallowing), as allowed by state regulations.
[f]This would include, for example, incorrect dilution or reconstitution, the mixing of drugs that are physically incompatible, and inadequate product packaging.
[g]This would include doses administered (1) via the wrong route (different from the route prescribed), (2) via the correct route but at the wrong site (e.g., left eye instead of right), and (3) at the wrong rate of administration.
[h]This would include, for example, administration of expired drugs and improperly stored drugs.
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Box 1. Common causes of medication errors (Reference 7).

- Ambiguous strength designation on labels or in packaging
- Drug product nomenclature (look-alike or sound-alike names, use of lettered or numbered prefixes and suffixes in drug names)
- Equipment failure or malfunction
- Illegible handwriting
- Improper transcription
- Inaccurate dosage calculation
- Inadequately trained personnel
- Inappropriate abbreviations used in prescribing
- Labeling errors
- Excessive workload
- Lapses in individual performance
- Medication unavailable

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addition, a systems analysis of ADEs found that the most common system defects included a lack of communication and readily accessible drug and patient information in a timely manner (References 12, 13). A later study reported the incidence of medication errors in hospitalized adults as 5.3 per 100 medication orders, with most errors being preventable and occurring at the point of ordering (References 14, 15).

Adverse drug events occur more frequently in pediatric patients than in adults (References 16–18). In 2001, the incidence of medication errors in pediatric patients was reported as 5.7 per 100 medication orders. Furthermore, these researchers classified medication errors as actual or potential errors. They found that most (79%) potential ADEs in children occurred at the stage of ordering, with most involving dosing errors. The most common drug classes included intravenous anti-infectives, electrolytes and fluids, and analgesics and sedatives (Reference 16). Subsequently, a Sentinel Event Alert aimed at preventing pediatric medication errors was issued by The Joint Commission (TJC), which reported that the most common types of errors in children include dosing error (37.5%), omission error (19.9%), wrong drug (13.7%), and prescribing error (9.4%). The most common causes include performance deficit (43%), knowledge deficit (29.9%), procedure/protocol not followed (20.7%), and miscommunication (16.8%) (Reference 17).

Vulnerability of Pediatric Patients

Pediatric patients pose a challenge to the standard medication use process (MUP) by introducing complex steps and specialized clinical decision-making skills. Limited drug information is available for pediatric patients, who often require off-label use of U.S. Food and Drug Administration (FDA)-approved medications and extrapolation of safety and efficacy data from adult literature. Commercially available drug formulations are often unsuitable for pediatric patients. As described below, these differences make infants and children more susceptible to medication errors and related injuries (Reference 16).

Developmental Differences

Pediatric patients can be further classified into neonates (term and preterm), infants, toddlers, children, adolescents, and adults on the basis of age. During each developmental stage, a pediatric patient has variable pharmacokinetic and pharmacodynamic parameters. Dramatic changes in both renal function and metabolism occur during the first year of life, posing unique challenges for health care providers when optimizing effectiveness and minimizing adverse effects. Neonates often experience significant changes in weight at least weekly, resulting in frequent calculations and dosing adjustments. Dosing is individualized on the basis of age, weight, or body surface area, requiring frequent calculation. Developmentally, smaller infants are unable to verbally communicate possible adverse events to caregivers, making it difficult to detect when an error has occurred.

Limited Buffering Capacity

Pediatric patients have a limited buffering capacity compared with adults, with less ability to compensate to avoid harm or injury when errors do occur. For example, a small dosing error in an adult may have minimal consequences or even go undetected; however, the same dosing error could be fatal in a neonate, especially for high-risk agents such as electrolytes or anticoagulants (References 19–21).

Lack of Commercially Available Dosage Forms

Drug formulations suitable for pediatric patients are not readily available from manufacturers. As a result, frequent manipulation of both oral and injectable commercial products is required. This most often includes oral extemporaneous preparations and stock dilutions. Manipulation of commercial products can lead to changes in bioavailability, stability, and sterility, increasing the risk of harm.

Oral Extemporaneous Preparations

The lack of available dosage forms suitable for infants and children proves challenging for pharmacies that service children. Furthermore, the liquid preparations

that are available by the manufacturer are often unpalatable. Specialized compounding, which is timely, is not done in all pharmacies. The lack of pediatric-specific dosage formulations is also a large burden on families and caregivers. It is not uncommon for parents or caregivers to be asked to open and empty capsules to sprinkle the contents onto food. Caregivers may also be asked to crush tablets, dilute them in water, and give an aliquot of this preparation to their child. This process has significant risk and potential for error, especially in families with limited education or language barriers. This emphasizes the importance of discharge teaching and targeted patient education.

Stock Dilutions

A dilution of a commercial product may be required to meet the needs of pediatric patients, especially the neonatal population. Dilutions are typically used for doses measuring less than 0.1 mL to improve accuracy during medication dispensing and administration. For example, furosemide is a common diuretic used in pediatric patients. The recommended dose of furosemide is 1 mg/kg/dose. If the patient weighs less than 1 kg, his or her dose will be too small to measure using the standard concentration 10 mg/mL available from the manufacturer. As a result, the drug needs to be diluted to 1 mg/mL. The dilution process requires careful calculation and manipulation, both of which have a potential for error. In addition, when a stock dilution is made to prepare many patient-specific doses, an error in the dilution process may affect many patients or an entire patient care unit.

Multiple Concentrations

The use of several concentrations for both oral and intravenous preparations can be confusing. Many drugs are available commercially in significantly different concentrations to meet the needs of very small infants as well as older children and adults. In fact, some medications are labeled "infant" or "pediatric" such as gentamicin, naloxone, and sodium bicarbonate. As a result, potential harm or injury can occur when the wrong concentration is used inadvertently. The result was fatal for the infants that received the wrong concentration of heparin and a 2-year-old girl whose life ended as a result of a compounding error when concentrated sodium chloride was mistaken for normal saline (References 19–21).

Similarly, dosing errors may also occur when using several concentrations, especially when doses are expressed in units of volume. For example, if the prescriber wrote a prescription for 1 teaspoon (5 mL) of amoxicillin, it would be unclear which commercially available concentration was to be dispensed—125 mg/5 mL, 250 mg/5 mL, or 400 mg/5 mL. If the prescriber wrote a prescription for 250 mg (5 mL) of amoxicillin, it would be clear that the 250-mg/5-mL concentration should be used. For methadone oral solution, dosing by volume may result in a 10-fold overdose if the prescriber does not adequately clarify the concentration to be dispensed. A 10-fold error with high-risk agents like narcotics or digoxin may result in significant injury or death.

For clarity, it is recommended that doses always be expressed in milligrams and milliliters—not just milliliters. Also worth noting is that, in the outpatient setting, the measuring of oral liquid preparations is inconsistent. For instance, some caregivers use oral syringes, cups, dosing spoons, or teaspoons for medication delivery, which results in variability of medication administration. It is important to consider this type of error and to ensure adequate understanding when providing patient/caregiver education. Community pharmacists play a large role in educating patients and caregivers about medications and their appropriate administration and use.

Medication Error Preventive Strategies

The Institute for Safe Medication Practices (ISMP) has established its role as a leader in medication safety education and preventive strategies. The ISMP has provided the framework for developing medication safety programs and has published several tools to help practitioners implement these strategies (References 2, 22–24). Distribution of safety newsletters encourages the reporting of error-prone practice patterns and actual medication errors using a collaborative approach. The ISMP has become an invaluable external reporting system for both institutional and community settings that tailor to the needs of pharmacy and nursing.

The Pediatric Pharmacy Advocacy Group (PPAG) is an international nonprofit professional pharmacy association dedicated to promoting safe and effective medication use in children through communication, research, education, and advocacy. In 2001, PPAG, in collaboration with the ISMP, published guidelines for the prevention of medication errors in pediatric patients (Reference 25). This collaborative identified medication safety strategies specific to pediatric patients, highlighting unique challenges in this vulnerable population. Specific recommendations included the use of technology, with consideration for pediatric-specific customization and medication management standards as well as the impact of unit-based clinical pharmacists in medication error prevention. These recommendations were endorsed by the American Society of Health-System Pharmacists (ASHP) in support of established standards for pediatric pharmacy practice (References 7, 26).

The American Academy of Pediatrics (AAP) also published a policy statement that included medication error preventive strategies and organizational principles to define and guide the health care system for pediatric inpatients. The AAP defined the role of the pediatrician in helping to develop multidisciplinary medication safety programs and support for a culture of safety (Reference 27).

In summary, these organizations endorse the medication safety preventive strategies promoted by the IOM, which include support for a culture of safety, additional training and education, medication management standards, patient-centered care, and the judicious use of technology. In the next section, some of these principles will be discussed as they pertain to pediatric pharmacy practice.

Culture of Safety

Transparency

The first step in medication error prevention is establishing a culture of safety within the organization, focusing on systems, as opposed to individuals, to improve safety. A transparent quality improvement strategy encourages ADE reporting and allows frontline staff to offer recommendations for improving processes to enhance safety, optimize resources, reduce costs, or provide better workflow and efficiency. It is vital that the organization support nonpunitive actions when errors occur or are reported as part of its culture. There are still some institutions where staff receive corrective action and disciplinary consequences when errors are recognized or reported. Although practitioners should be held accountable, organizations should concentrate on system failures as opposed to individual performance. Errors are seldom the result of practitioner negligence. A high priority for each organization should be to establish best practices within the MUP to support its employees and minimize risk.

A Systems Approach

The MUP consists of several steps including research and development, procurement, prescribing, transcribing, dispensing, administration, monitoring, and documenting. Figure 2 provides a summary of each step in more detail (Reference 28). The likelihood of error increases with each step in a process, especially when humans are involved. Human error, known as an active failure, occurs because of a single failure point within a system. An example of an active failure is nonadherence to policy or procedure. However, most errors occur as a result of several failures within a system called latent failures. Latent failures differ from active failures because they lie dormant within the system and often go undetected until an error occurs. These are considered the weaknesses or gaps of the system. Other tools used to evaluate risk or determine why an error occurred include failure mode effects analysis (FMEA) and root cause analysis (RCA). An FMEA is often performed prospectively to determine latent failures. This is usually done as a gap analysis for complex systems or processes within a system before an event occurs. An RCA is typically done retrospectively because of an event to determine the cause and effect of an actual error (References 29–31). As described below in more detail, system failures in training or education, standardization, communication, complexity, and limited technology may also increase the risk of medication errors.

Training and Education

Organizations should develop age-based training and education programs that promote basic competencies required for pediatric pharmacy practice. Providing essential age-specific training to practitioners in areas such as developmental pharmacology, common drugs and disease states, medication safety, and pediatric-specific considerations establishes a basic foundation for practitioners who care for infants and children.

Pediatrics should be a required therapeutics course in the curriculum of schools of pharmacy. In academia, pediatrics is often an abbreviated course with minimal content, or it may only be offered as an elective course. Some pharmacy students are never exposed before graduation to the unique challenges and differences of pediatrics and medication therapy (Reference 32). Residency training is often necessary to gain the foundational knowledge base and clinical decision-making skills to apply to pediatric pharmacy practice. The development and expansion of residency programs in any organization can help promote pharmacy services that are more focused on pediatric patients. There are fewer pediatric pharmacy residency programs compared with more generalized pharmacy practice residency programs and other specialties. Some institutions provide only 1 year of training as either pediatric pharmacy practice or a higher-level specialty residency. Some institutions offer both a pharmacy practice and specialty residency program in pediatrics. This provides a more comprehensive pharmacy practice and specialized residency training experience, with additional exposure in a particular subspecialty (e.g., neonatal intensive care unit, critical care, oncology) after pharmacists complete 2 years of residency training in an exclusively pediatric environment.

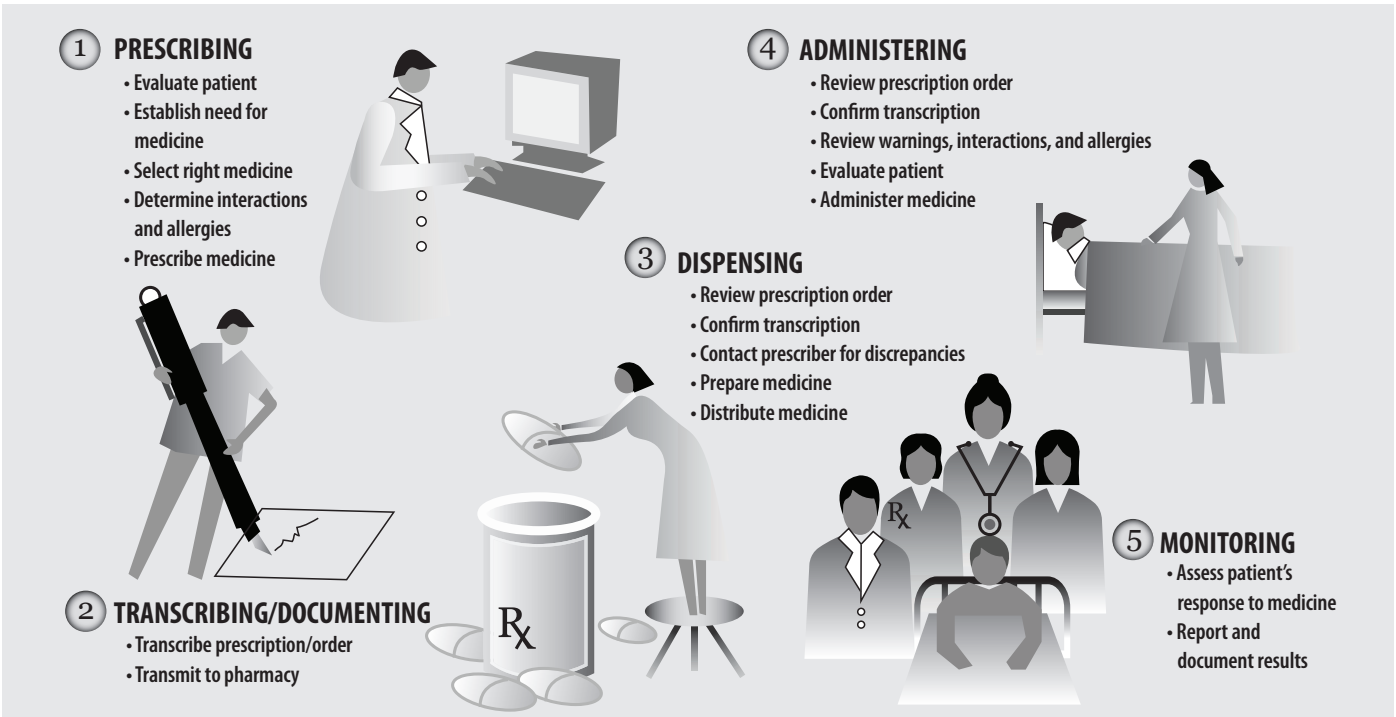


Figure 2. Medication use process (Reference 28).

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Medication Management Standards

The Joint Commission has established medication management standards that provide a basic framework for medication error prevention (References 33, 34). These standards, in conjunction with the national patient safety goals, provide guidance in drug ordering, administering, storage, and dispensing to optimize the MUP. Box 2 summarizes a checklist for organizations as a tool for evaluating medication management in the pediatric population (Reference 17).

A formulary management system provides a framework to establish safe and cost-effective medication use. Pharmacy must play a large role in formulary selection, procurement, management of drug shortages, and medication use evaluation. A standard approach to drug request and review for formulary consideration should be established. This should include, at a minimum, important efficacy and cost data, any potential safety implications, and similar formulary medications that can be removed (References 35, 36).

Several tools have been developed to aid in standardizing medication use. The ISMP serves as a resource for clinical practice and as a liaison to the manufacturers in recommending improved drug delivery systems and relabeling or renaming a look-alike/sound-alike (LASA) drug. These include a standardized drug nomenclature (i.e., tall man lettering), problem-prone abbreviations and confusing drug names (i.e., LASA), and, most recently, standardized concentrations for neonates (References 37–39). In addition to these tools, other medication error prevention strategies to promote safety should be established. This might include a process for medications that look or sound alike to be stored separately to prevent confusion.

The ISMP has also identified an extensive list of high-alert medications including anticoagulants, narcotics, insulin, neuromuscular-blocking agents, intravenous digoxin, dialysis solutions, and total parenteral nutrition. These drugs are more often associated with significant harm if used in error. Strategies recommended to improve safety with these agents include limiting access, making use of auxiliary labels and alerts, making independent double checks, and using standardization throughout the MUP (Reference 40).

The Joint Commission emphasizes the use of standardized concentrations and patient-specific medication dispensing in the most ready-to-administer form. These best practices are challenging for pediatric institutions where medication orders are complex with limited standard doses, and frequent manipulation of drug formulations are required to meet the needs of the patient. If comparing the doses dispensed for adults with the volume of pediatric workload, the additional steps in the dispensing process, including time, are often unaccounted for as part of the workload data. In addition, appropriate weight-based dosing must be verified

Box 2. Evaluation checklist for medication management in pediatric populations (Reference 17).

The following checklist is not meant to be comprehensive. Organizations may use it as a model, adding items based on recommendations from government agencies or professional associations.

- Protocols for drug evaluation, selection, storage, and administration are standardized for the pediatric population.
- Concentrations and dose strengths of high-risk medications are limited and standardized.
- When adult medications are used off-label for children, the drugs are prepared and dispensed in patient-specific "unit doses" or "unit-of-use" containers.
- A pharmacist reviews and verifies all pediatric medication orders (except in emergency situations).
- A pharmacist with expertise in pediatric medications is on-call at all times.
- Up-to-date references for pediatric medications are readily available in all areas where children may be treated.
- All pediatric patients are weighed at the time of admission.
- Weight is always recorded in kilograms.
- No high-risk drug is dispensed to a pediatric patient unless he or she has been weighed (except in emergency situations).
- Medication orders/prescriptions are standardized, and the guidelines for inclusion of all necessary information are enforced.
- If a computerized physician order entry system is used, it has been adapted to pediatric populations and provides alerts if necessary information is missing, a dose adjustment is required, and so on.
- Adult and pediatric doses or medications are stored separately, and products that have been repackaged for pediatric use are clearly labeled as such.
- Barcoding technology (if applicable) has been adapted to pediatric codes, such as small-volume, patient-specific dose labels.
- All staff who may be involved in the care of children receive specialty training, including medication risks and double checks to reduce those risks.
- Staff who educate parents and other caregivers about patients' medications include all necessary information about side effects, administration method, and so on.

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for all inpatient and outpatient orders. These additional steps in the dispensing process should be considered when allocating resources, although they are difficult to quantify scientifically.

Patient-Centered Care

Patient-centered care provides a comprehensive approach to medical management by incorporating all members of the health care team, with a focus on patients and their families/caregivers. Clinical pharmacists have emerged as providers in comprehensive drug management to patients and providers by optimizing medication therapy, monitoring for effectiveness and adverse effects, and promoting health, wellness, and disease prevention. Studies have shown that clinical pharmacy services improve patient outcomes and reduce cost (References 16, 41, 42). Establishing safe medication practices has also become the primary role of pharmacists, and ownership of continuous quality improvement efforts and measurement of medication safety are mainstays of current practice.

Unit-based clinical pharmacists establish a model for more comprehensive and patient-focused care. This approach has shown reductions in medication errors in both adult and pediatric patients through the provision of more accessible drug information, patient education, and medication reconciliation, together with other clinical pharmacy services (References 16, 41, 42).

Most recently, the ASHP Pharmacy Practice Model Initiative provided a summary of recommendations to advance pharmacy practice to meet the needs of changing health care systems. As part of this initiative, key stakeholders and leaders in pharmacy collectively established a blueprint for establishing pharmacists as having a direct patient care role. As drug therapy experts, pharmacists must leverage technology and clinical skills to optimize patient care and improve safety, focusing on drug therapy management (Reference 43).

Implications of Technology

Implementation of technology provides a safer environment for patients through standardization of the MUP. This includes the use of computerized prescriber order entry (CPOE) with clinical decision support systems (CDSS), electronic medical records, pharmacy systems, automated dispensing cabinets (ADCs), smart infusion pumps, and barcode medication administration (BCMA). The ISMP offers self-assessment tools and guidelines to help organizations implement new modes of technology and evaluate existing systems for areas of improvement compared with best practices and national standards. However, many of the advances in commercial technology are marketed to adult patients; thus, caution and careful consideration must be used when

implementing them in the pediatric setting. In the following section, each of these tools and their impact on medication safety will be summarized, with pediatric considerations highlighted.

Computerized Prescriber Order Entry

Computerized prescriber order entry has been established as a key piece of technology to reduce medication errors and has been endorsed by several leading patient safety organizations since the initial IOM reports were published. Although increasingly more common within the health care community, the implementation of CPOE remains a challenge. When implemented correctly, CPOE requires a reasonable timeline, resources, and capital funding, which are often barriers to progress. In addition, the use of CDSS and forced functions with CPOE is essential to provide necessary drug-drug and drug-allergy interactions, drug information, dosing recommendations, and warnings or alerts to ensure best practices of prescribers while using the tool. Forced functions allow a more streamlined approach to medication ordering, assisting in drug selection and dosing. For example, a drug that is only provided as an oral dosage form should not be orderable as an injection (Reference 44).

Studies in adults support CPOE as an important tool in medication error prevention (References 45, 46). Overall, CPOE provides more legible and complete medication orders with limited use of abbreviations. However, in pediatrics, data are limited and sometimes conflicting (References 47–54). One study found that medication prescribing errors and rule violations were almost eliminated and that potential ADEs were reduced 41% in critically ill pediatric patients (Reference 49). Another study found that CPOE implementation resulted in increased mortality, with subsequent studies showing conflicting results (References 50–52). In critically ill neonates, CPOE implementation has shown improved safety and reductions in medication prescribing errors (Reference 54). Box 3 summarizes factors associated with an "ideal" CPOE system (Reference 25).

Advanced clinical decision support tools provide additional guidance to the prescriber beyond what typically comes with the commercial software license (Reference 55). Examples include order set development and standardized ordering pages for error-prone medications (e.g., continuous infusions, total parenteral nutrition, patient-controlled anesthesia, anticoagulation), patient-specific code dosing sheets, P&T (pharmacy and therapeutics) initiatives, drug shortage alerts, FDA warnings and safety alerts, and customized dosing advisers. Alerts displayed to the prescriber should be carefully reviewed, monitored, and minimized to those requiring specific action or considered significant. Computerized prescriber order entry systems should have an established standard nomenclature that aligns with best practices established by the ISMP and TJC. For example, the CPOE system should not allow trailing or leading zeros or abbreviations and should include tall man lettering as a system standard. Patient weight should only be entered using the metric system—kilograms, instead of pounds—which is often the source of dosing errors. In summary, CPOE with clinical decision support targets the most error-prone step of this process, ordering and prescribing, and reduces medication prescribing errors. Of importance, success is often related to a well-executed implementation plan and the feasibility of customization from the commercial software. Customization is essential to success in pediatrics, and pediatric-specific resources will need to be allocated for long-term development and maintenance.

Pharmacy Systems

Ideally, the pharmacy verification system interfaces with the CPOE system, which eliminates the need to transcribe medication orders and supports a "paperless" process. For order verification, it is important for the

Box 3. Functionality associated with an "ideal" CPOE system (Reference 25).

- Prescriber order entry for verification by nurse and pharmacist
- Computer-generated medication administration records
- Current medication list that is readily accessible
- Two-way interface between pharmacy and other electronic documentation tools
- Access to archived patient information
- Age- and weight-based dosing recommendations
- Allergies and weight required and forced-upon order entry
- Access to vital patient information at the point of order entry
- Clinical decision support which provides appropriate patient-specific drug information (e.g., dose checks, allergy alerts, renal function, drug interactions and contraindications, laboratory warnings)
- Provide forced functions by limiting inappropriate options for order entry based on the drug that is ordered.

CPOE = computerized prescriber order entry.
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pharmacy system to require minimal manipulation of medication orders. For pediatric patients, most orders that are verified require frequent manipulation, which sometimes results in miscellaneous orders or other workarounds to accommodate the specific needs of these patients. This process introduces risk and often takes time away from other clinical pharmacy services and responsibilities.

Automatic dispensing cabinets help standardize the dispensing process at the unit level, providing quicker access to select medications. Consequently, however, the storage of LASA and high-alert medications may introduce risk, so consistent use of medication error prevention strategies should be established. Medications approved for override need to be monitored and approved through a formal process. Patient profiling and scanning on restock are both important aspects of the ADCs that should not be overlooked because they provide additional safety within the process.

Barcode Medication Administration

Medication administration errors are difficult to intercept and have the most potential for harm. Barcode medication administration is recommended as a tool to improve medication safety during drug delivery. This tool provides emphasis on the five patient rights: right patient, right drug, right dose, and right route, at the right time. A recent survey found that around 30% of hospitals nationwide have implemented BCMA, a significant improvement from less than 10% in 2005 (References 56, 57).

The benefits of BCMA on medication errors have not been well established in adult or pediatric patients (Reference 58). Recent studies have shown reductions in medication errors of between 27.3% and 87%, but a significant return on investment has been difficult to quantify (Reference 59). It is important to understand specific barriers and other obstacles in nursing workflow because these often create workaround or frustration with the system. Some researchers have studied the use of BCMA in several hospitals, identifying 15 workarounds by nursing. Also reported were 31 causes of these workarounds to BCMA. These causes included unreadable barcode labels, missing or unreadable armbands, malfunctioning scanners, non-barcoded medications, failing batteries, uncertain wireless connectivity, and emergencies (Reference 60).

For pediatric patients, specific limitations of the system and other considerations need to be evaluated before implementation. For example, it is difficult to scan the armband of a swaddled neonate requiring temperature regulation in an incubator bed. In addition, barcoding from the manufacturer, which is the concept for the accuracy of these systems, is tailored specifically to adult dosage forms. Many of the pediatric formulations are not conveniently available from the manufacturer; therefore, each institution must establish its process for patient-specific barcodes and be able to provide the resources to maintain this process.

Smart Infusion Pumps

Smart pump technology provides a safety net for appropriate medication administration of intermittent and continuous infusions. Pharmacists play an essential role in drug library development, which provides the guardrails for safe drug delivery. These parameters are based on published drug dosing recommendations and established clinical practices within the institution. Most companies offer electronic data collection to allow periodic review for continuous quality improvement. This provides a summary of drug use and clinical practice patterns. The number of overrides of the guardrails can be monitored, which helps identify questionable practices or the need to adjust the library to avoid unnecessary alerts. More importantly, the drug library can be customized to meet the needs of the institution and promotes the use of standardized concentrations. Pediatric settings often require more than one standard concentration to meet the needs of the large variability in size within the pediatric population. This requires a larger and more customized drug library compared with that in adult settings. This should be considered upon initial implementation, and resource allocation should be evaluated for the development and maintenance of subsequent updates.

Measuring Medication Safety

It has been challenging for organizations to measure and track medication safety and methods to show the positive outcomes of specific improvement strategies. There are no standard medication safety indicators, and there is no suggested benchmark. Markers of performance, core measures, patient outcome data, regulatory and compliance standards, continuous quality data from technology (such as alerts and overrides), and medication events can be considered part of a medication safety program. For institutions that have implemented the use of technology, compliance with these systems and possible workarounds that need to be addressed may be considered.

Voluntary reporting is one way to identify potential failures within the MUP and make suggestions for improvement. However, reporting is solely voluntary and is significantly underestimated. Less than 5% of ADEs are actually reported through this process, and near misses are seldom included (Reference 61). Near-miss data help identify error-prone steps in a process before an event occurs. Occurrence reports should never be discouraged or used as a means to quantify medication error rate. Incident reporting should be rewarded as part of a nonpunitive, just culture with the goal of increasing voluntary

reporting. Trending of these reports reflects the state of the culture versus how safe a system might be; therefore, the goal is always to increase reporting through a nonpunitive system.

Occurrence reporting, when used in conjunction with other methods, is helpful in identifying vulnerability and risk within the MUP as part of a medication safety program. Adverse drug event surveillance tools, pharmacovigilance, and direct observation are more reliable in capturing ADEs (References 61–65). The use of known "triggers" to identify ADEs is effective and provides a way to prioritize patients on the basis of risk. These tools help provide more accurate and timely data in determining whether patients have experienced an ADE. Through a validated methodology and retrospective chart review, these events help determine system failures and opportunities for improvement. Unfortunately, this process is time-consuming and costly and still accounts for a small percentage of actual ADEs. An electronic "trigger tool" can provide real-time aggregate data by surveillance of all patients against the "triggers" without timely and costly chart review. The ADE surveillance provides additional utility to the framework of medication safety programs when used in collaboration with occurrence reporting and external reporting systems.

Conclusions

Medication errors occur commonly, and most are preventable, with pediatric patients at highest risk. Infants and children offer unique challenges and developmental differences that make this population more vulnerable. Their needs require additional steps in the MUP and complex clinical decision-making skills. Promoting a culture of safety and systems approach to medication errors are necessary in developing medication safety programs. Additional training and education in the area of pediatrics will provide the necessary foundation of knowledge. For pharmacists, this includes age-based competencies or additional didactic and residency training in basic pediatric pharmacy practice. Pharmacists trained in pediatric pharmacy practice are essential for appropriate patient care of both outpatients and inpatients. Community pharmacists provide dose checking and unique dosage forms for pediatric patients, as well as patient/caregiver education. Clinical pharmacists providing consistent clinical services in an inpatient setting should be available at the unit level to the multidisciplinary team in support of patient-centered care. Technology provides a standardized approach for error-prone steps in the MUP such as ordering and medication administration. When used judiciously, technology has the potential to enhance patient safety. Because most systems are developed for adult patients, additional resources must be allocated to customize and maintain technology systems to meet the unique needs of pediatric patients. Noncompliance and workarounds to the use of this technology should be evaluated to avoid unintended consequences and address vulnerabilities within the system. In addition, alerts and warnings should be kept to a minimum to avoid alert fatigue. Pharmacists play a key role in medication error prevention. Careful attention to the unique needs and vulnerability of pediatric patients should be a focus for patient safety standards and goals of national and regulatory agencies to provide children's hospitals the resources and governance needed to create a safer culture and environment.

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CHAPTER 5

Communicating with Children, Adolescents, and Their Caregivers

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Verbal and written communications are essential components of health care that help ensure adherence to therapy, patient safety, improved outcomes, and patient satisfaction. Health care providers are trained in communication techniques for adults, but they often state that they do not have as much experience communicating health information to children. Although many principles of communicating with adults are also applicable to children, communicating with children requires a different approach that considers the developmental level of the child as well as the child–caregiver interaction. Because children are often dependent on an adult to assist with medication administration, it is important that adults receive education unique to their child to increase their confidence in the treatment. If the health care provider shows interest, takes the time to answer questions and address concerns, and involves the child in the communication, parents are more likely to be satisfied with the care received and to adhere to the prescribed treatment (References 1, 2).

It is as important to talk with children about their medications as it is to talk with their parents. However, community pharmacists report that they talk with children about their medicines only 20% to 30% of the time (References 2, 3). Medication education for children can occur in many settings including community pharmacies, hospitals, clinics, group education visits, schools, and health fairs. This chapter will review the benefits associated with communicating with children about medicines as well as techniques for delivering age-appropriate information and gaining rapport with this unique population; moreover, this chapter will provide tips for educating parents about their children's medicines.

Communication to Decrease Errors and Improve Adherence

Once the medicine leaves the pharmacy, it is the responsibility of the parent and the child to ensure appropriate dosing and administration. As evidenced by previous studies, medical visits, and calls to poison control centers, many unintentional overdoses occur each year because of improper measurement and accidental ingestion. Difficulty measuring the proper dose could result from low health literacy or a simple misunderstanding of the directions. Studies have shown that without intervention, only 50% of caregivers give an accurate dose of liquid medicines to the children in their care (Reference 4). This number can be increased to 95% using a 1- to 3-minute intervention of demonstrating how to use a dosing device, having the caregiver demonstrate use of the device, and providing pictogram-based information handouts (Reference 4). One study also concluded that the additional education resulted in an improved adherence rate of 62% to 91%.

In another study, parents were asked to measure 1 teaspoon or 5 mL of acetaminophen by a dosing cup, a dropper, a dosing spoon, and an oral syringe (Reference 5). When a dosing cup was used, most doses measured resulted in an overdose. This study also concluded that dosing errors with cups and dosing spoons were more common in parents with lower health literacy. Pharmacists should be aware of the challenges that caregivers face in administering medications and be proactive in providing information and appropriate dosing devices as well as ensuring caregivers' understanding of the medication and its administration.

General Communication Principles for Children and Adolescents

Children can generally begin providing and receiving information during health care visits at age 3 years, with an even greater level of involvement starting at age 7 years (Reference 6). However, many children have become accustomed to being silent observers during health care visits and may develop disinterest in or resentment toward their health care. The United States Pharmacopeia has developed a position statement outlining the principles for teaching children and adolescents about medicines (Reference 7). Included in those principles are that children want to know about medicines, so health care providers should be communicating directly with them about what they want to know as well as what they need to know. In addition, children should be encouraged to ask questions about medicines. An encounter with a child should always end with a question resembling "What questions do you have for me about your medicine?"

Communication with children can be for obtaining information, expressing empathy, relaying information, or confirming understanding. Each of these requires age-specific techniques that provide age-appropriate information and establish rapport as discussed in the following sections.

Cognitive Developmental Stages

An important consideration when communicating with children is ensuring the message is delivered at a level they can understand. Identifying a child's developmental stage can help narrow the scope of information to be communicated and improve efficiency and effectiveness. One of the methods used to help identify a child's developmental stage is Piaget's classification of cognitive development. The four stages of cognitive development are as follows: sensory motor, preoperational, concrete operational, and formal operational. Table 1 describes Piaget's developmental stages and the ways in which to apply them to those receiving medication education. When applying any system for staging a child's developmental level, it is important to recognize that the stages are estimates and that they vary between patients. As children are exposed to situations and experiences, they may more quickly enter a new developmental stage than other children who have not had the same experiences (Reference 6). In addition, traditional methods of staging development do not apply to children with learning disabilities or disease states that impair development (e.g., autism spectrum disorders). Each child should be assessed individually for his or her level of development and educated at that level.

Developing Rapport

Many children and adolescents are hesitant to talk to adults they do not know. Therefore, you should attempt to gain trust and let children know you are interested in them as individuals. General tips recommended to adults communicating with children of all ages include the following (Reference 8). (1) Sit at their eye level. (2) Begin by discussing something that is of interest to them. (3) Avoid commenting on characteristics about which they may be self-conscious (e.g., hair color, height, shyness). (4) Use a normal tone of voice. (5) Do not talk down to them. (6) Maintain a calm demeanor. (7) Give them your attention. (8) Listen actively. Additional items are summarized in Box 1. Consideration should always be given to differences in culture that may affect a person's likelihood of maintaining eye contact and his or her interest in self-care.

Infants

The importance of gaining rapport starts in infancy. Although it is not possible to deliver medication education to infants, interacting with an infant's parents will be much easier if the infant is at ease. Adults should not lean over an infant's face or take the child from his or her parents if the infant is anxious about leaving his or her parent's arms. In addition, an adult should not force play with an infant. If the infant is interested in playing, he or she will reach out or make sounds. If the infant is distressed, he or she will likely become more anxious if you attempt to play with him or her. It can often be difficult to communicate with parents when their infant is irritable; thus, giving parents time to comfort their infant will be beneficial.

Toddlers and Preschoolers

From ages 1–5, children are developing new skills and do not understand the importance of health care visits and listening to others. They often have difficulty communicating because they are learning new words and learning how to formulate sentences. Therefore, when obtaining information from them, patience is necessary to give children time to think about and communicate a sentence. When they become distracted or disruptive, a playful distraction, such as an opportunity to draw or play with a toy, is helpful to redirect them to a new activity. Because they do not have a good concept of time, it is important to avoid asking for a prolonged recall of information. Information should be delivered in simple terms, with brevity and honesty.

Box 1. General tips for communicating with children and adolescents (References 7, 8, 10, 12).

- Sit at or below their eye level.
- Begin by discussing something of interest to the child or adolescent.
- Remain calm and nonjudgmental.
- Be aware of their body language and respond if needed.
- Speak in a normal tone of voice.
- Allow them to express concerns and ask questions.
- Give them ample time to respond to questions.
- Give them your full attention.
- Listen attentively and repeat to ensure you understand them.
- Allow them to participate in decision-making about their medicines.

Table 1. Piaget's Cognitive Developmental Stages and How They Affect Medication Education (References 8, 9)

Approximate Age (years)	Developmental Stage	Features	Medication Counseling
0–2	Sensory motor	Do not see the connection between self and outside objects	Learning about medicines is not possible.
2–7	Preoperational	Can consider only a single aspect of a situation Can consider only the here and now Have no concept of cause and effect Have difficulty conceptualizing time Do not understand the connection between an action and their health Can use symbols or pictures to represent objects	Hands-on activities are the most effective. It is important to include the taste of medicine in your education to them. Example information to provide: This medicine will keep you from getting sick. You will take it when you wake up in the morning and before you go to sleep at night. Your mom or dad will help you take the medicine.
7–11	Concrete operations	Can focus on many aspects of a situation Can think about concrete events but have difficulty with hypothetical situations Can distinguish between self and effects of the outside world Can best understand concrete or observable situations Can understand that diseases are preventable Can see things from different points of view	Give them time to ask questions, and explain concepts to them. Include a discussion about the adverse effects of medicines that should be reported to parents. Example information to provide: This medicine will go into your lungs and make it easier for you to run and play. You will take it when you wake up and before you go to bed. If you do not take it two times a day, it will not work. You need to brush your teeth after using the medicine. Work with your mom and dad to make sure you take the medicine right and remember to take the medicine.
≥ 12	Formal operations	Capable of hypothetical thought and logical reasoning Understand how illness occurs and is affected by their actions Begin to understand they can have control of their health	Typically able to receive a message at the same level as an adult, but keep in mind they may be more embarrassed by certain topics. Example information to provide: This medicine works in your lungs to decrease mucus and swelling so that you can breathe better and have less cough. Because you are breathing things into your lungs every day that cause the problem, this medicine works only if used every day, twice a day. It is important to keep using this medicine even when you start feeling better because the asthma will still be there. Work with your parents to help make this part of your everyday routine.

School-Aged Children

At this age, it will be easier to obtain information from children using open-ended questions and allowing them to explain how they perceive a situation. They will begin to provide a more accurate recall of symptoms and activities, and they will often give a more accurate account of their current symptoms than their parents. Because they have a better understanding of cause and effect by this age, they will have a greater need to know information and to have a chance to express their concerns and questions. School-aged children can begin contributing to the decision-making process about their treatment plan. If they state they do not like a medicine, they should be offered alternatives to choose from and educated on how the alternatives differ. Children at this age respond well to visual displays of disease states and medications and enjoy interacting with adults by way of games and challenges.

Adolescents

Adolescents are the least likely to trust that adults have their best interest in mind and may be unwilling to provide a great deal of information. It is important to begin the conversation by asking about something that may be of interest to them rather than starting with your agenda. If they feel their viewpoint is not being considered or understood, they are likely to withdraw or even become angry. Before rapport is established, many adolescents will not maintain eye contact. This will improve as their trust in the provider increases.

The adolescent should be the primary person giving information during an encounter, and the parents should be asked to confirm or add information. It is important that they learn to advocate for their own health care and learn to communicate their needs. Adolescents will often provide information that may alarm or shock the provider. Of importance, remain calm and nonjudgmental in these circumstances. When developing a treatment plan, it is critical to include adolescents in the decision-making process and affirm that their questions and concerns have been addressed.

Adolescents should be given an opportunity to talk with their health care provider in private. If you plan to ask adolescents about contraception, sex, alcohol, drug, or tobacco use, it is better to speak with them in private than in a parent's presence. This will allow them more comfort to speak freely and will let them know you have respect for their privacy and perspective. Common situations that require privacy and sensitivity when communicating with adolescents include counseling on the proper use of contraception, on drug interactions that may increase the risk of unintended pregnancy while using oral contraception, and on interactions between alcohol and medications. Adolescents may be unwilling to talk about these issues in a first encounter, but they are likely to become more open after trust is developed in follow-up encounters. Parents may resist, but it is important to emphasize that adolescents need to learn to communicate with the provider and begin to take responsibility for their medical care.

Additional Communication Considerations for Children and Adolescents

The technique and skill required for obtaining information differs from that required to deliver information. When obtaining information, open-ended questions are preferred. However, the questions must be specific and often need to be followed up with more straightforward, closed-ended questions. With closed-ended questions, children and adolescents may give responses that they think will make the provider happy (Reference 10). The provider may need to let them know it is acceptable to be honest. An example of a statement to help encourage truth in recalling medication adherence is this: "A lot of people have trouble remembering to take their medicine; do you find it hard to remember to take your medicine?" This can then be followed by more open-ended questions to obtain further details.

Children often refer to a medicine by appearance or color, and sometimes, they refer to it by what they use it for rather than by name. When interviewing the patient, if the child does not know the name of the medicine, it is important to ask if he or she can describe what it looks like. The pharmacist can then emphasize the importance of knowing the medication name and assess recall at future visits.

When providing medication information to children, it is important to select the most salient points and deliver them using the principles discussed in the previous sections. Studies have confirmed that children want to know the following information about their medicines (Reference 11):

1. How does the medicine taste?
2. When do I take the medicine?
3. How will it make me feel better?
4. How long will I take it?
5. What are the adverse effects?
6. Why am I taking the medicine?

Other important points to emphasize include informing children to tell an adult if they take too much medication or see someone else taking their medicine and encouraging them to tell an adult if they have any new feelings or adverse effects while taking the medicine.

When asking a child or adolescent to demonstrate a skill such as inhaler technique, smaller children may be fearful, embarrassed, or shy. Children who are fearful or anxious may be given the spacer to play with before

trying to demonstrate the technique so that they can learn that it is not a harmful object. For those who seem embarrassed, it is important to ensure as much privacy as possible and consider demonstrating the technique yourself before asking them to do so. It is also important to give children and adolescents choices—when a choice truly exists. For example, you do not want to ask, "would you like to show me how you use your inhaler?", if you intend to have them show you, even if their answer is "no." Rapport will be lost if you proceed with having them demonstrate the technique after they have responded that they are not interested. A more appropriate statement might be, "I need to watch you use your inhaler so I can make sure it is working; would you like to show me now or after we talk about your medicines?"

Effective techniques to assist children with medication adherence are patient-specific. Children and adolescents should be asked what they believe would help them remember to take their medicines because no single approach works for everyone. Potential methods to assist in remembering include posting dosing calendars with or without medication pictures on them, providing cell phone reminders or alarms, placing the medications in an area of high visibility, and using pillboxes.

Communicating with Parents

Studies have shown that parental satisfaction with medical care is determined by the practitioner's interpersonal skills. Parents who feel they were not treated with respect or that their fears were not addressed will be dissatisfied and less likely to follow through with medical advice (Reference 12). In interviews of parents during physician visits, 88% wanted to be addressed by their names rather than as "mom" or "dad" (Reference 13). Pharmacists are encouraged to ask parents how they prefer to be addressed. There is a fine balance between including the child in the encounter and ensuring that the parents feel included as well. It is helpful to let parents know that you plan to ask the child questions and provide them with information before starting. Box 2 provides a summary of items to consider when talking with parents or caregivers.

Box 2. General tips for communicating with parents (References 7, 8, 10, 12).

- Inform them you will be talking with their child or adolescent.
- Learn their names, and use their names during communication.
- Provide guidance on how much involvement the child should have in administering his or her medication.
- Encourage them to provide their child with some autonomy when appropriate.
- Allow them to express concerns and ask questions.
- Respond respectfully about any misconceptions or irrational fears they may express.

Box 3. Information needed to supplement medication information handouts.

- How to measure the dose
- How to administer the medicine
- How the adverse effects may manifest in a child
- How the warning labels apply to a child
- Reassurance that the medicine may be used for an indication other than those listed

Written information dispensed with prescriptions is not phrased with a child in mind and can be frightening and confusing to parents. Many parents fear giving their children any medicines; thus, reading this information may cause them not to give the medicine. An example is the use of fluoroquinolones in children. The American Academy of Pediatrics recommends the use of fluoroquinolones in children if other alternatives do not exist for treatment of infection. However, many patient information handouts will state that these medications should not be used in children because of the lack of an FDA label-approved indication and because of safety concerns. Parents who see this information may be resistant to giving the medicine to their child unless they are educated on the data that exist and informed that no alternative exists. In addition, written information should be at the sixth-grade reading level to ensure understanding by those with low health literacy. It is estimated that most materials are written at a 10th- or 11th-grade reading level (Reference 14). Methods of assessing readability include the Flesch-Kincaid formula and McLaughlin's Simplified Measure of Gobbledygook. The United States Pharmacopoeia has developed a guide to assist in developing and evaluating educational materials (Reference 15). This guide includes not only readability, but also the balance of words and pictures and the appropriateness of content for the child's age. Parent-friendly medication information handouts are available that are more specific to children and are easier to read (Reference 16). These handouts are available in English or Spanish. Lexi-Comp online also provides pediatric-specific patient education handouts in 18 different languages. If these resources are unavailable, it is important to point out differences that may be relevant to the child compared with the information provided on the medication handout from the pharmacy. Examples are provided in Box 3. In addition, parents

may need assistance in determining how the information contained in a warning label may apply to their child. For example, the statement "do not operate heavy machinery while taking this medicine" has a different meaning for a child. In this case, parents should be counseled that their child should avoid tall playground equipment and should be careful riding his or her bicycle or any motorized toys while taking that medicine.

It is also important to determine who will be giving children their medicine. It is often given at school or by a grandparent, or it may be given at another house if the parents do not live together. If the person accompanying the child to the visit is not the only one to administer the medicine, he or she should be educated on the importance of providing all information to anyone who will be responsible for giving the child's medicine. Too often, children are held responsible for transporting medicines between homes and remembering to take them, putting them at risk of not receiving the medicine consistently. Adequate information should be provided to the school to ensure the safe and appropriate administration of the medication in that setting.

Another important component of a health care encounter is to verify the identity of the person with the child. It is possible that another relative, a babysitter, or a stepparent will be with the child. In some cases, it may be necessary to contact the parents if they are not at the visit to ensure they have the information they need to safely use the medicine for their child. This practice will also help avoid uncomfortable moments that occur when the identity of the adult is assumed.

Conclusions

Children and adolescents are important consumers of health care and should be provided the information they need to use medications safely and effectively. Pharmacists play an important role in communicating with children, adolescents, and their caregivers. The techniques discussed in this chapter will help facilitate effectiveness and efficiency in communicating with this unique population. With practice, communicating with children and adolescents will become a rewarding experience and will positively affect the health and safety of these vulnerable patients.

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CHAPTER 6

Drug Formulations

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Learning Objectives

1. Know the legislative actions undertaken by the U.S. Congress to encourage the pharmaceutical industry to conduct drug trials supporting pediatric labeling of their drugs and develop a pediatric formulation.
2. Understand the need for extemporaneous formulations in infants and children.
3. List the most common extemporaneously compounded oral liquid formulations.
4. Know the different extemporaneous options available for providing a suitable dosage form for a child.
5. Know the methods involved in compounding an extemporaneous formulation and the factors that affect its use in clinical practice.

Abbreviations in This Chapter

ASHP	American Society of Health-System Pharmacists
FDA	U.S. Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
PREA	Pediatric Research Equity Act
USP	United States Pharmacopeia

Introduction

An estimated 74.5 million children, 0–17 years of age, resided in the United States in 2009. Of these, 21.3 million were 5 years or younger (References 1, 2). In December 2010, the *Wall Street Journal* reported that according to Medco Health Solutions, one of the largest U.S. pharmacy benefits providers, around 25% of children and 30% of adolescents between 10 and 19 years of age were taking a medication for a chronic condition in 2009 (Reference 3). Almost 7% of these were taking two or more drugs for long-term therapy. It was determined that the total number of prescriptions or refills dispensed to children and teenagers were as follows (from most to least): asthma drugs 45,388,000; attention-deficit/hyperactivity disorder drugs 24,357,000; antidepressants 9,614,000; antipsychotics 6,546,000; antihypertensives 5,224,000; sleep aids 307,000; oral hypoglycemic drugs 424,000; and statins 94,000. Many of these drugs, however, are not labeled for use in the 0- to 9-year-old age group and thus are not available in suitable dosage forms.

Research and development of most pharmaceuticals are focused on providing safe and efficacious drugs for adults. Initial efficacy and safety trials for most drugs often exclude infants, children, and pregnant women. Drugs routinely used in pediatric patients may not have U.S. Food and Drug Administration (FDA)-approved pediatric labeling. Without these trials, information regarding the effective dose per patient weight (milligram per kilogram per dose), the frequency of dosing, and the adverse effects of a drug in the pediatric population may come from pilot observations, from case reports or series, and by trial-and-error methods. Drugs without pediatric labeling are often unavailable in dosage forms suitable to administer to children. For example, tacrolimus is used as an immunosuppressive agent in adult and pediatric solid-organ and peripheral stem cell transplants. However, it is available only as a capsule. A liquid formulation has to be extemporaneously compounded for use in infants and children.

In 1997, the Food and Drug Administration Modernization Act (FDAMA) was signed into law (Public Law 105-115) (Reference 4). According to Section 111, pharmaceutical companies with a drug already on the market or submitting a new drug application to the FDA were offered an additional 6 months of patent protection (exclusivity to market that drug) in exchange for conducting requested trials in children. The goal was to encourage the pharmaceutical industry to conduct trials supporting the pediatric labeling of their drugs and develop a pediatric formulation for their product. In 2002, the FDAMA was reauthorized as the Best Pharmaceuticals for Children Act, and in 2007, it was signed into law (References 5, 6). Under this law, the FDA would accept, on a case-by-case basis, pediatric labeling directions for producing extemporaneous pediatric formulations as an alternative to a stable commercial formulation.

In 1998, the FDA mandated an assessment of new drugs, new indications, new dosing regimens, new active ingredients, and new dosage forms for pediatric patients, which in 2003 was formalized as the Pediatric Research Equity Act (PREA). In 2007, PREA was reauthorized. As of 2007, more than 130 products have received new pediatric labeling directions, but only 8% have new pediatric formulations, and another 8% provide information

on the preparation of suspensions or recipes for extemporaneous compounding (Reference 7). Despite the submission of pediatric studies by the industry, 22% of the products were not approved by the FDA for use in children for reasons such as "ineffective dosing, overdosing, ineffective drug action, or previously unknown side effects" (Reference 7). Thus, BPCA and PREA have had a limited impact on meeting the need for pediatric formulations of drugs commonly used in children. Both BPCA and PREA were introduced into Congress in March 2012 for reauthorization.

Need for Extemporaneous Formulations

A pharmacist may need to compound an oral extemporaneous formulation for pediatric and adult patients unable to swallow solid dosage forms or receiving their medication through a nasogastric tube or gastronomy tube. In addition, most children younger than 6 years, even when given specific training, are unable to swallow a solid dosage form such as a tablet or capsule (References 8, 9). Most pediatric drug doses are based on body weight (milligram per kilogram per dose) or body surface area (milligram per square meter per dose). Such individualized doses cannot be easily administered and titrated using the available solid dosage forms, which contain a fixed amount of drug, but they can be accurately and easily administered using a liquid formulation. For drugs requiring drug concentration monitoring (e.g., tacrolimus), dose adjustments to achieve safe and effective blood concentrations may result in doses that are not commercially available. However, such drugs can be provided to this patient population by extemporaneously compounding a liquid formulation of a suitable concentration using the commercially available solid dosage forms. In addition, the presence of an inactive ingredient or a high concentration of the inactive ingredient in a commercially available liquid dosage form may prevent the use of a particular drug in premature or full-term neonates (e.g., dexamethasone intensol containing 30% alcohol). Toxicity may not be observed after a single dose of this medication; however, toxicity because of the long-term administration and additive effects of alcohol from other concurrently used alcohol-containing drugs cannot be ignored.

Pharmacists also compound parenteral drugs extemporaneously. Parenteral drugs are supplied in a commercially available ready-to-use concentration, a concentrated solution requiring further dilution, or a dry, lyophilized powder for reconstitution. Some intravenous drugs (e.g., phenobarbital, morphine, furosemide, fentanyl) may be too concentrated for accurate measurement of the small doses (volumes) needed for treatment of neonates and infants. These doses may require further dilution before intravenous administration. For example, furosemide is available as a 10-mg/mL solution for injection. A neonate weighing 0.7 kg would require a dose of 0.7 mg intravenously or 0.07 mL, which cannot be accurately measured with the commercial formulation. Under these circumstances, the intravenous drug requires further dilution with a suitable diluent to prevent errors in measuring the amount. The drug stability and sterility of this parenteral extemporaneous formulation must be documented before its use in patients.

Most Commonly Prepared Pediatric Extemporaneous Formulations

Information regarding the most commonly compounded extemporaneous formulations for children in the United States is available through surveys published in the literature. A 1998–1999 survey of 57 small and large hospitals caring for pediatric patients identified the five most commonly compounded formulations as follows: spironolactone, captopril, ursodiol, metronidazole, and allopurinol (Reference 10). Oral, nasogastric, and gastric were the most common routes of administration of these medications. The same survey also identified 103 drug formulations prescribed by pediatricians that had no compounding and/or stability information.

In 2009, another survey was conducted to determine the scope and frequency of use of extemporaneous liquid formulations in children's hospitals (Reference 11). The five most commonly compounded formulations in 20 pediatric U.S. hospitals identified by this survey were lansoprazole, spironolactone, captopril, sildenafil, and ursodiol. This survey identified a total of 231 drugs or drug combinations that were compounded into liquid formulations for 28% of all inpatient admissions during a 12-month period.

Options for Meeting Extemporaneous Formulation Needs

Pharmacists who frequently compound extemporaneous formulations will need informational resources providing formulation recipe, compounding method, storage conditions, and stability data. The most common and immediate resource is the United States Pharmacopeia (USP) (Reference 12). It contains official monographs of compounded preparations that include valid stability data to establish a beyond-use or expiration date. Compounding information supported by stability studies and beyond-use dates may be available in the package insert of drugs such as losartan, benazepril, lisinopril, and rifampin. This information usually is included in the package inserts of brand-name products because, most often, the manufacturer has a pediatric labeling for the drug.

Tertiary publications such as the *Pediatric & Neonatal Dosage Handbook*, which was designed as a dosing reference for neonates, infants, and children, and NeoFax, which is a reference specific for the dosing and

administration of drugs in neonates, contain necessary information regarding the extemporaneous compounding of a drug formulation (References 13, 14). *Pediatric Drug Formulations* and *Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients* are two tertiary publications that compile information regarding formulation recipes, methods of compounding, storage conditions, and stability data (References 15, 16). Primary peer-reviewed publications regarding specific formulations can be obtained by conducting a literature search through PubMed using search terms such as "extemporaneous drug formulations," "extemporaneous compounding," and "extemporaneous preparations children," combined with the name of drug being researched.

Another resource for locating information about the compounding of extemporaneous formulations is the Investigator's Brochures or reports, but these are usually not easily available or accessible because of their confidential or proprietary nature. Before using the compounding information from the Investigator's Brochures or pharmaceutical industry–generated reports, pharmacists should ascertain that the formulation stated in the brochure is not being investigated for its stability, bioavailability, or bioequivalence through ongoing clinical trials. If such trials are under way, the formulation cannot be dispensed for routine patient care until trial results indicate successful achievement of the study goals. Manufacturers of the solid dosage forms can be contacted to obtain information regarding any preclinical testing of extemporaneous formulations. However, when a drug does not have pediatric labeling, the potential for legal liabilities may prevent manufacturers from providing information about formulations used in preclinical studies.

When compounding and stability information for an oral commercially manufactured product is unavailable, some pediatric hospital pharmacies may compound it as a suspension or solution. The liquid preparation is usually packaged in a tight, light-resistant container (amber plastic bottle) and stored at controlled temperatures to observe for signs of physical changes. For water-containing formulations prepared from solid ingredients, the USP-recommended beyond-use date is no later than 14 days for liquid preparations when stored at cold temperatures between 2°C and 8°C (Reference 17). The USP recommendations should be used with caution, especially because the stability of a drug in liquid depends on several physicochemical properties such as pH and oxidation-reduction reactions. For example, captopril (0.75 mg/mL) in cherry syrup is only stable for 2 days at room temperature or when refrigerated, and it is stable for 10 days or less in a 1:1 mixture of Ora-Sweet and Ora-Plus or Ora-Sweet SF and Ora-Plus, depending on the storage temperature. Thus, without the stability data, labeling these captopril formulations with a beyond-use date of 14 days according to the USP would be inappropriate (Reference 18). Under these circumstances, preparing powder papers or using dosage forms intended for adults with or without alterations seems to be a logical option. The procedure for preparing powder papers includes crushing the tablets or opening the capsules, uniformly redistributing the contents with inactive ingredients such as lactose to achieve the required dilution, weighing out each powder paper, and then folding it. This is time-consuming and labor-intensive. In addition, the contents of the powder paper will still have to be reconstituted into a liquid before administration. Solid dosage forms without an extemporaneous formulation can also be administered by splitting or crushing a tablet and opening a capsule and administering the content with food. These modifications may result in a compromise in the physicochemical stability of the drug, an altered rate of drug absorption, and improper dosing because of the inaccurate splitting of tablets or spillage during reconstitution or mixing with a large amount of food that is not completely ingested by the patient. For a solid dosage form with a water-soluble active ingredient, crushing the tablet or mixing the contents of a capsule with a specified amount of water and drawing up the exact amount for a dose can be done. However, this process can be time-consuming and has the potential for calculation errors. Alternatively, the injectable solution of the same drug can be administered orally, provided both formulations contain the same salt form with similar bioavailability. However, the cost of the injectable solution can be a limitation to using this method.

Methods of Preparing Different Extemporaneous Formulations

The most commonly compounded extemporaneous formulation for children involves making a liquid formulation from a solid dosage form. This could be a solution or a suspension. For a more comprehensive review of preparing safe and effective extemporaneous formulations, the authors refer the reader to the American Society of Health-System Pharmacists (ASHP) Web site and other valuable resources (References 19, 20). The ASHP Web site provides guidelines that address areas of extemporaneous compounding through the following documents: (1) ASHP Technical Assistance Bulletin on Compounding Nonsterile Products in Pharmacies (Reference 21) and (2) ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products (Reference 22).

A suspension is the most commonly compounded oral formulation because most drugs (active ingredients) are not completely water soluble. Even when the active ingredient is completely water soluble, the inactive ingredients (excipients) may not be soluble. A suspending agent that can uniformly suspend the active and inactive ingredients after shaking for a time is necessary to

accurately withdraw a dose and should be used in the compounding recipe. Adding a suspending agent to a formulation with soluble active but insoluble inactive ingredients allows a more pharmaceutically elegant preparation. Without a suspending agent, the insoluble ingredients will settle rapidly. This may result in the caregiver's inaccurate assumption that he or she is unable to withdraw a uniform dose from the preparation. Preparation of an extemporaneous liquid dosage form from tablets involves crushing and triturating them in a mortar into a fine powder while capsule contents are emptied into a mortar and mixed well. The powder is then levigated into a smooth paste using small portions of the selected vehicle. This selected vehicle usually consists of a combination of a suspending agent and a sweetening agent. The uniform paste is mixed with the rest of the vehicle in geometric proportions with constant mixing until the desired volume is almost achieved. The mixture is then transferred to a measuring device (graduated cylinder), and the selected vehicle is added to make up the required volume according to the recipe. The preparation should then be transferred to an appropriate container, such as an amber bottle, and labeled with a beyond-use date under storage conditions, as indicated in the stability studies. Prescription bottles should not be used as measuring devices because the graduation marked on these bottles is inaccurate.

Ingredients (raw materials) used in compounding extemporaneous formulations should always be of USP or equivalent grade. Carboxymethylcellulose and methylcellulose are common suspending agents. A carboxymethylcellulose sodium suspension is easier to compound, but it has a pH of about 10. The preparation of a methylcellulose suspension is difficult and time-consuming. However, the advantage of using a methylcellulose 1%/simple syrup suspension (1:1) is that it is an inert, nonreactive, and pH-neutral (pH 6.8) vehicle. Most pharmacists in the United States prefer to use commercially available ready-to-use vehicles. A vehicle can be easily prepared by combining Ora-Plus (Paddock Laboratories, Minneapolis, MN), a carboxymethylcellulose-containing suspending agent, with Ora-Sweet (Paddock Laboratories) syrup, in a 1:1 volume. Ora-Sweet SF (Paddock Laboratories), a sugar-free syrup vehicle, can be used instead of Ora-Sweet. All three have an acidic pH, which should be considered in compounding suspensions when drug stability data are unavailable for the preparation. Ora-Blend and Ora-Blend SF, marketed by the same manufacturer, are sweetened (with sugar or sugar free) suspending agents, eliminating the need to prepare a 1:1 mixture of Ora-Plus with Ora-Sweet or Ora-Plus with Ora-Sweet SF. Other available vehicles include SyrSpend SF (Gallipot, St. Paul, MN), SyrSpend SF Alka, SyrSpend SF Cherry, SyrSpend SF Alka Cherry, SyrSpend SF Grape, and SyrSpend SF Alka Grape.

Certain characteristics of an oral liquid dosage form such as taste, odor, palatability, texture, color, and sweetness may enhance a patient's acceptance of his or her medication therapy. Children usually prefer a sweet taste with fruity flavors. Choice of flavoring agents may also depend on the characteristic taste of the drug itself because certain flavoring agents mask certain tastes well. Cocoa-flavored vehicles may mask bitter-tasting drugs, whereas fruit or citrus flavors may mix well with sour or acidic-tasting drugs, and salty drugs can be made more palatable if masked by raspberry- or orange-flavored vehicles. Formulations can be made to taste sweet using vehicles such as Simple Syrup USP or Ora-Blend. Flavored vehicles such as SyrSpend SF Cherry or SyrSpend SF Grape can also be used. Adding a flavoring agent to an extemporaneous formulation when it was not used in the original formulation could alter the stability and concentration of the medication. If additional flavoring is needed, the agent can be added to each dose immediately before administration of the dose. Adding coloring agents may make the formulation esthetically more appealing. However, the stability of the formulation may be affected by the presence of these chemical coloring agents because most of the dyes are affected by the formulation pH, presence of oxidizing or reducing substances, or exposure to light. Thus, many institutions do not add coloring agents to extemporaneous formulations.

Factors That Affect the Use of Extemporaneous Formulations in Clinical Practice

Stability

A stable extemporaneous formulation is one that retains the characteristics and properties it possessed at the time of preparation throughout its storage and use (i.e., shelf life). An extemporaneous formulation should be physically, chemically, microbiologically, therapeutically, and toxicologically stable during its shelf life. Stability is affected by temperature, radiation, light, humidity, particle size, pH, water and other solvents, container properties, and other chemicals that may be present in the formulation. All compounded preparations require a beyond-use date labeling (i.e., the date beyond which a compounded preparation is not to be used, which it is determined from the date of preparation). Several factors determine this beyond-use date.

The expiration date for a commercially manufactured product cannot be directly extrapolated to assign a beyond-use date for a nonsterile preparation compounded from it.

Physical stability includes the lack of change in color, odor, taste, texture, and consistency of the preparation. This can be tested by storing the compounded formulation at various commonly used storage conditions (temperatures and containers) and periodically (e.g., at weeks 0, 1, 2, 4, 8, and 12) testing for components of physical stability. The most common storage temperatures for medications include room temperature (20˚C–25˚C), refrigerated temperature (2˚C–8˚C), and freezer temperature (-25˚C to -20˚C). Storage containers generally consist of amber plastic prescription bottles unless specified in the stability studies.

Chemical stability of drugs in an extemporaneous formulation (both sterile and nonsterile) involves the measurement of the active ingredient(s) to ensure its potency during storage and use. During storage, no more than a 10% change in the active ingredient concentration should occur. Pharmacists should consult and apply specific and general stability documentation and literature when available. Testing for chemical stability involves the use of certain analytic methods. The analytic method should be accurate, efficient, specific, reproducible, and stability-indicating. No single method can be used to test all drugs. Many analytic tests are not available in the pharmacy or a health care facility; thus, they may need to be outsourced to contract laboratories. A contract laboratory chosen for conducting analytic tests should follow USP General Chapter standards using official methods and techniques for testing. The chemical stability of the active ingredient(s) is usually reported as a percentage of the initial concentration. In general, formulations with storage conditions and beyond-use dates, which preserve the potency of the active ingredient(s) within 90% to 110% of the initial concentration, should be used; however, the USP monograph for the specific drug should be consulted for acceptable variance for each active ingredient being evaluated.

Most pharmacies involved in dispensing extemporaneous formulations will lack the resources to undertake such chemical stability studies. Instead, they may have to rely on books, peer-reviewed publications, or a commercially available or institution-specific computer database with recipes for extemporaneous formulation recipes. A search of the literature for stability data on an extemporaneous formulation may reveal several studies using different compounding agents, storage conditions, and duration of stability for the same drug. All stability data must be carefully interpreted with respect to the particular compounded formulation. Ease and convenience of compounding, duration of stability of the formulation, easy availability of the compounding ingredients, and cost are factors to consider in choosing a particular recipe as your institution's primary formulation for a compounded product. Formulations with limited demand and a shorter duration of stability should not be prepared in large amounts to avoid waste of unused medications.

Because most extemporaneous liquid preparations are aqueous, they are at risk of contamination with microorganisms that can multiply during storage. These microbes may include molds, yeasts, and bacteria. The susceptible preparations should be protected using preservatives. An effective preservative should be non-toxic, inhibit the growth of microorganisms likely to contaminate the preparation, be sufficiently water soluble to achieve the necessary concentration, be in an ionized form to penetrate the microorganism, be nonirritating and nonsensitizing, have adequate stability, be compatible with all the other ingredients of the formulation, and be nonreactive with the container and closure used to dispense the formulation. The most commonly used preservatives include derivatives of benzoic acid such as sodium benzoate and methylparaben and derivatives of sorbic acids such as potassium sorbate. Ora-Plus contains potassium sorbate and methylparaben. If the alcohol content in alcoholic and hydroalcoholic extemporaneous formulations is sufficient to prevent microbial growth, these may not need additional chemical preservatives. However, a high alcohol content may preclude the use of these products in certain pediatric patients, especially premature neonates and newborns. Necessary caution must be used while compounding so that the pH is not altered and the preservative is not diluted below its effective concentration.

Sterility

Sterility testing is required for compounded parenteral products. All hospitals are required to comply with the USP's Revised General Chapter <797> Pharmaceutical Compounding—Sterile Preparations Guidelines, which set practice standards to ensure that compounded sterile preparations are of high quality and prevent harm or fatality to patients caused by microbial contamination, excessive bacterial endotoxins, and errors caused by the presence or absence of labeled ingredients or presence in inaccurate amounts (Reference 23). Most pharmacies involved with the compounding of sterile preparations have undertaken major renovations to their "Clean Rooms" while actively training and evaluating their personnel in aseptic manipulation skills. The guidelines assign compounded sterile preparations three risk levels on the basis of their probability of microbial contamination and physical and chemical contamination. These risk levels (low, medium, and high) refer to the quality of the compounded sterile preparation immediately after the final aseptic manipulation or immediately after the final sterilization. These guidelines offer pre-administration exposure duration and temperature limits (beyond-use date and storage temperature) in the absence of direct testing results or appropriate information sources that

justify different limits. For a more comprehensive review of sterility requirements for extemporaneously compounded parenteral formulations, the authors refer the reader to the USP's Revised General Chapter <797> Pharmaceutical Compounding—Sterile Preparations Guidelines (Reference 23).

Efficacy and Safety of Extemporaneous Formulations

The ultimate goal of preparing an extemporaneous formulation is to make it effective and safe in patients. Care must be taken to maximize safety; for example, a sustained-release tablet should not be crushed when preparing a liquid formulation, and a preservative such as benzyl alcohol should be avoided in a formulation intended for a neonate. Propylene glycol, ethanol, and sorbitol are examples of other excipients that have been associated with adverse effects in pediatric patients and should be avoided in pediatric formulations. Ideally, extemporaneous formulations should be studied in patients to establish their efficacy and safety. However, such studies are generally cost-prohibitive because of lack of funding for the performance of clinical studies. Efficacy and safety data of an extemporaneous formulation obtained in adult studies may not be reproducible in a pediatric population because of specific characteristics of the formulation. Omeprazole, a proton pump inhibitor, is often administered by a nasogastric tube for stress ulcer prophylaxis in critically ill mechanically ventilated patients. An extemporaneous suspension of omeprazole in sodium bicarbonate is formulated to prevent degradation of the drug granules by the gastric acid. This suspension has been effective in preventing clinically significant upper gastrointestinal bleeding in critically ill adults, and it effectively maintained excellent control of the gastric pH (References 24, 25). In a study of mechanically ventilated critically ill pediatric patients, administration of the same extemporaneous suspension did not produce the expected gastric acid suppression, despite the use of recommended standard doses (Reference 26). The inadequate amount/volume of bicarbonate in the smaller pediatric dose to protect omeprazole degradation from the acid in the child's stomach was hypothesized to cause this difference in bioavailability and efficacy.

A concern about the use of many extemporaneous formulations is lack of bioavailability, efficacy, and safety data in pediatric patients. However, their use should be guided by justified need, application of principles discussed in this chapter, and documentation of stability data, which are increasingly available and shared within the professional community. Despite the lack of specific efficacy and safety studies, extemporaneous formulations should be prepared using general principles already discussed in this chapter. Each formulation should be made specifically based on available data. For example, variations in the use of drug and excipients, method of preparation, and storage conditions can compromise stability as well as the expected efficacy and safety of the formulation. Patients receiving extemporaneous formulations should be monitored to ensure they achieve the expected clinical benefit and experience no untoward effects. Clinical experience should be shared through presentations at national meetings, discussions on Web sites, and publications in peer-reviewed journals. With the exception of nonsterile or contaminated products, safety concerns have seldom been reported with the use of extemporaneous formulations. Although no specific agency or group receives reports of adverse events associated with extemporaneous formulations, such occurrences should be reported to the FDA and be widely shared with health care professionals.

Cost

Reimbursement for the preparation and dispensing of extemporaneous formulations can be difficult, especially for community pharmacies, based on the patient's insurance carrier. Insurance authorization is often required, and the process can be time-consuming. For each extemporaneous formulation, the total cost includes the cost of the active ingredient(s), other ingredients needed to compound the formulation such as vehicles, and the pharmacist's compounding time. Reimbursement may not cover all the costs, especially if expensive ingredients such as injectables are needed. Thus, pharmacists preparing extemporaneous formulations should inquire with insurance carriers to determine how they will be reimbursed. Specialty pharmacies involved in compounding various extemporaneous formulations do not usually accept health insurance and will directly bill the patient for the total cost of the extemporaneous formulations.

Conclusions and Future Perspectives on Development of Pediatric Drug Formulations

The need for extemporaneous formulations will continue to exist both for new drugs under patent protection and for generic drugs. Pharmacists play an essential role in the preparation of stable, effective, and safe formulations for pediatric patients of all age groups. However, the challenge of finding adequate information and financial resources for conducting stability and sterility as well as efficacy and safety studies with all extemporaneously prepared formulations of new and generic drugs is likely to continue. The use of these preparations should

be monitored for efficacy and safety in patients, and these data should be shared through presentations at national meetings and publications in journals and books. Finally, funding agencies should provide resources to conduct studies with extemporaneous formulations to make important drugs accessible to infants and children as well as to adult populations with special needs.

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CHAPTER 7

Pediatric Toxicology

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Learning Objectives

1. Discover the methods of poisoning data collection and how they affect prevention and therapy efforts.
2. Evaluate the incidence of pediatric poisonings in the United States on the basis of the National Poison Data System Annual Report.
3. Evaluate the poisoned child.
4. Assess the efficacy of gastric decontamination methods.
5. Manage select pediatric poisonings.

Abbreviations in This Chapter

AAPCC	American Association of Poison Control Centers
AC	Activated charcoal
FabAV	Crotalidae polyvalent immune Fab antivenom
MDAC	Multiple-dose activated charcoal
NAC	*N*-acetylcysteine
NAPQI	*N*-acetyl-*p*-benzoquinonimine
SOI	Syrup of ipecac
WBI	Whole bowel irrigation

Introduction

Despite increased educational efforts, childhood poisonings remain a common occurrence, though not a common cause of morbidity and mortality in this population (Reference 1). Each year, more than 2 million toxic exposures are reported, with more than one-half of them occurring in children younger than 6 years. Medical management of poisoned children is similar to that of adults, but there are important differences that need to be considered. This chapter will introduce the reader to the reporting system used to document epidemiologic trends in toxic exposure incidence and management, the evaluation of the poisoned child, decontamination principles, and the management of selected poisonings.

Epidemiology

National Poison Data System

The National Poison Data System is the only comprehensive resource in the United States for poisoning surveillance. It is owned and managed by the American Association of Poison Control Centers (AAPCC), and since 1983, the organization has used these data to publish an annual report (Reference 2). The current database holds data on around 50 million reported toxic exposures. Poison centers, typically staffed by pharmacists and nurses, serve all 50 states and several U.S. territories (poison specialists are available 24 hours/day and can be reached through the national poison hotline at (800) 222-1222). They provide data to the National Poison Data System from incoming calls by an online reporting system that allows real-time surveillance of poisoning data. In 2009, poison centers received almost 2.5 million calls for human exposures. In 1983, there were just over 250,000 calls, though for the past 15 years, the number has been more than 2 million (Reference 2). Of note, the database contains information from reported exposures only; many more exposures occur that are unreported, including those that cause serious injuries or fatalities (Reference 3). In addition, some clinicians manage poisonings without consulting a poison center, whereas therapeutic errors that result in toxicity may not be reported (References 1, 2). Nevertheless, these data are very important because they can help inform policy decisions in many areas, including direction of toxicology research; drug formulation safety and development; appropriateness of drugs for over-the-counter status; direction of health care professional education and poison prevention education for the general public; and detection of chemical and bioterrorism incidents (Reference 4). A wealth of information for health care professionals and the lay public regarding epidemiology, prevention, and management of poisonings is available at Web sites provided by the AAPCC and the Centers for Disease Control and Prevention (www.aapcc.org/dnn/Home.aspx and www.cdc.gov/HomeandRecreationalSafety/Poisoning/index.html).

Epidemiologic Trends

Historically, children younger than 6 years have accounted for about one-half of all reported exposures. In 2009, children younger than 3, 5, and 20 years accounted for almost 40%, 52%, and 65% of reported toxic exposures, respectively (Reference 2). Despite these high percentages, children account for only a small minority of fatalities, with less than 2% occurring in children younger than 6 years in 2009 when the toxin contributed in some way to death (total fatalities in this age group

as a percentage of all reported fatalities have decreased from 6.3% to 2.4% since 1985). In addition, a vast majority of exposures in children up to age 12 years have resulted in no to minor effects (Reference 2).

The type of poisons most often encountered by children has remained much the same for many years. Analgesics, cosmetics, and household cleaning substances are consistently the most common toxins encountered overall. In addition, foreign bodies, topical preparations, vitamins, antihistamines, cough and cold preparations, pesticides, and plants are often ingested (Reference 2).

Evaluation of the Poisoned Child

For many reasons, an infant, toddler, or young child will ingest or be exposed to substances that an older child or adolescent will not. As children age, they become more mobile, allowing them to satisfy their natural curiosity and investigate things they could not before. They can mimic adult activities such as taking medicine. They may mistake pharmaceuticals such as ferrous sulfate for candy or household cleaning products for flavored drinks. Fortunately, in children, most exposures are without intent to harm, and most result in minimal, if any, adverse outcomes (Reference 2). However, any time a child presents with an altered level of consciousness, metabolic disturbance, neurologic dysfunction, or cardiac or pulmonary distress, it is important to include toxic exposure as part of the differential diagnosis (Reference 5). In many ways, the evaluation of a poisoned child is similar to that of an adult, but there are some important differences in supportive care, history, and evaluation.

Supportive Care

Supportive care, always a key component in managing toxic exposures, begins with airway stabilization and should follow Pediatric Advanced Life Support guidelines (Reference 6). Some substances, such as tricyclic antidepressants, can cause rapid loss of consciousness and result in the need for rapid sequence intubation for airway protection, ventilation, and oxygenation. In addition, early antidote administration may be necessary, such as naloxone in opioid ingestions. Table 1 lists antidotes to selected poisonings. A more complete listing of available antidotes has been provided elsewhere (Reference 7).

History and Physical Examination

A thorough history of ingestion in small children is usually easier to obtain than in adolescents. In general, caregivers provide as much detail as possible, including ingested volume estimates, tablet counts, containers of the substance in question, and a complete review of toxic substances in the vicinity of the child when the exposure occurred. The toxin involved and the time of ingestion are easiest to ascertain, whereas the amount ingested is typically more difficult to determine. These factors are important because they significantly affect the decision to implement decontamination strategies (Reference 8). It is important to inquire about other places the child may have been because more than 10% of toxic ingestions in children occur outside the home (Reference 1). A thorough history in an adolescent patient can be more difficult because the ingestion is more

Table 1. Antidotes for Selected Poisonings or Toxicities (References 7, 10)

Antidote	Poisoning or Toxicity
Atropine/Pralidoxime	Organophosphates/Carbamates
Dantrolene	Malignant hyperthermia caused by the disease process such as neuroleptic malignant syndrome or heat stroke; or caused by drug toxicity such as from monoamine oxidase inhibitors or baclofen withdrawal
Deferoxamine	Iron
Digoxin antibody fragments (Fab)	Digoxin
Flumazenil	Benzodiazepines
Edetate calcium disodium (EDTA)/dimercaprol (British Anti-Lewisite or BAL)/succimer (dimercaptosuccinic acid)	Lead
Methylene blue	Methemoglobinemia
Protamine	Heparin
Sodium and amyl nitrite/sodium thiosulfate	Cyanide
Sodium bicarbonate	Salicylates, tricyclic antidepressants
Vitamin K	Warfarin

likely intentional or the result of substance abuse, and these patients may not be as forthcoming. Any information obtained from the patient about the ingestion must be taken in context of the clinical condition of the patient (Reference 1). Other important contrasts between children and adolescents or adults are as follows: children more often present within a few hours of ingestion; multiple toxins are more likely involved in adolescent or adult exposures; in children, the toxin is more likely nontoxic; and children ingest a smaller amount in most instances (Reference 1). Although children more often encounter nontoxic substances or ingest an amount that results in minimal harm, there are several toxins or drugs that may cause serious harm or death in very small amounts (References 1, 9) (see Table 2).

The physical examination centers on mental status and vital signs, including pulse; respiratory rate, quality, and effort; blood pressure; temperature; skin tone and color; hydration status; peripheral pulses; and perfusion (Reference 10). A neurologic examination should be performed, including an evaluation of pupil size and reactivity. Many signs and symptoms of toxic exposures manifest in clusters called toxidromes (see Table 3). Specific toxins, identified from the history or presentation, may allow the caregiver to narrow the physical examination to focus on expected or possible complications of the poisoning.

Laboratory Evaluations

Laboratory evaluations should be directed by the history and physical examination, though most patients

Table 2. Substances That May Result in Severe Toxicity in Children with Small Exposure (References 1, 9)

Substance	Potentially Significant Exposure in Children	Definitive Management or Antidote Beyond Supportive Care and Decontamination
Antihistamines	Diphenhydramine – 10–15 mg/kg	Benzodiazepines for seizures or delirium Sodium bicarbonate for arrhythmias
Benzocaine	¼ teaspoon of 7.5% gel in infants ½ teaspoon in older children	Methylene blue for methemoglobinemia
β-Adrenergic antagonists	Propranolol > 4 mg/kg (40-mg tablet in 10-kg infant)	Pressor support Glucagon, insulin, glucose for cardiovascular support
Calcium channel blockers	Diltiazem > 1 mg/kg	Calcium Pressor support Glucagon, insulin, dextrose for cardiovascular support
Camphor	5 mL of camphorated oil (1 g of camphor)	Airway management Seizure management
Clonidine	0.1 mg Chewing clonidine patch	Pressor support Arrhythmia management Seizure management Naloxone
Diphenoxylate/ atropine	> 0.5–2 tablets	Naloxone
Methyl salicylate	> 150 mg/kg Several salicylate sources 1 mL of oil of wintergreen = 1400 mg of acetyl-salicylic acid	Dextrose and electrolytes Forced diuresis/alkalinization Seizure and cerebral edema management
Opioids	Hydrocodone 2.5 mg reported lethal in infants (1 teaspoon of hydrocodone/ acetaminophen solution)	Naloxone Pressor support Seizure management
Sulfonylureas	Chlorpropamide – 250 mg Glipizide – 5 mg Glyburide – 2.5 mg	Intravenous dextrose Glucagon
Tricyclic antidepressants	10–20 mg/kg considered potentially lethal in infants and young children	Sodium bicarbonate, lidocaine, phenytoin, or magnesium for arrhythmias Seizure management

Adapted with permission from McGraw-Hill. Fine JS. Pediatric principles. In: Flomenbaum NE, Goldfrank LR, Hoffman RS, Howland MA, Lewin NA, Nelson LS, eds. Goldfrank's Toxicologic Emergencies, 9th ed. New York: McGraw-Hill, 2011:447.

Table 3. Toxic Syndromes

	Vital Signs								
Group	**BP**	**HR**	**RR**	**T**	**Mental Status**	**Pupil Size**	**Peristalsis**	**Diaphoresis**	**Other**
Anticholinergics	-/↑	↑	±	↑	Delirium	↑	↓	↓	Dry mucus membranes, flush, urinary retention
Cholinergics	±	±	-/↑	-	Normal to depressed	±	↑	↑	Salivation, lacrimation, urination, diarrhea, bronchorrhea, fasciculations, paralysis
Ethanol/sedative hypnotics	↓	↓	↓	-/↓	Depressed, agitated	±	↓	-	Hyporeflexia, ataxia
Opioids	↓	↓	↓	↓	Depressed	↓	↓	-	Hyporeflexia
Sympathomimetics	↑	↑	↑	↑	Agitated	↑	-/↑	↑	Tremor, seizures
Withdrawal from ethanol/sedative hypnotics	↑	↑	↑	↑	Agitated, disoriented, hallucinations	↑	↑	↑	Tremor, seizures
Withdrawal from opioids	↑	↑	-	-	Normal, anxious	↑	↑	↑	Vomiting, rhinorrhea, piloerection, diarrhea, yawning

BP = blood pressure; HR = heart rate; RR = respiratory rate; T = temperature.↑= increases; ↓ = decreases; ± = variable; - = change unlikely.

Reprinted with permission from McGraw-Hill. Flomenbaum NE, Goldfrank LR, Hoffman RS, Howland MA, Lewin NA, Nelson LS. Initial evaluation of the patient: vital signs and toxic syndromes. In: Flomenbaum NE, Goldfrank LR, Hoffman RS, Howland MA, Lewin NA, Nelson LS, eds. Goldfrank's Toxicologic Emergencies, 9th ed. New York: McGraw-Hill, 2011:34.

presenting with suspected poisoning should have serum chemistries and acid-base status assessed. If the history indicates the possibility of alcohol ingestion, serum osmolality may be useful. Ingestions of cardiovascular agents such as β-adrenergic blockers or calcium channel antagonists warrant an electrocardiogram (Reference 5). A chemistry allows a calculation of the anion gap [(Na – {Cl + HCO_3}); normal value 4–12 mEq/L]. An elevated gap may indicate poisoning. A common mnemonic device to identify potentially causative mechanisms of an elevated anion gap is MUDPILES (M = methanol; U = uremia; D = diabetic ketoacidosis; P = propylene glycol; I = isoniazid, iron, infection; L = lactic acidosis; E = ethylene glycol, ethanol; S = salicylates) (Reference 10). Serum concentrations of acetaminophen (and, to a lesser extent, salicylates, ethanol, or iron) should be strongly considered because acetaminophen is so widely available in many products, and symptoms may not occur until several hours postingestion. Other specific serum concentrations are generally not required and should be dictated by the specific ingestion (Reference 5).

Decontamination

Although gastric decontamination offers the only therapy available other than supportive care for many orally ingested poisons, there are few data to suggest any effect on outcomes. Reasons for this include significant inter-patient variability (even in similar ingestions) and that most ingestions result in only minor to moderate adverse effects. Very large trials would be required to detect differences in outcome. This is especially true in children (Reference 11). The lack of evidence of efficacy has resulted in significant decreases in the use of gastric decontamination. In 1985, syrup of ipecac (SOI) or activated charcoal (AC) was given in almost 20% of child exposures, whereas in 2009, only 1.5% of children received these agents (Reference 2). This trend has also been influenced by statements from the American Academy of Pediatrics and the American Academy of Clinical Toxicology (References 12, 13). The American Academy of Pediatrics statement, a summary of the evidence for managing poisoning in the home, suggests that SOI not be used routinely in the home and that insufficient evidence exists to recommend use of AC in the home. The American Academy of Clinical Toxicology statement notes that evidence for improved outcomes with use is lacking and that use should typically be limited to patients who ingest a toxic substance up to 1 hour before administration. Table 4 summarizes gastric decontamination methods, but a brief discussion of each is provided in sections that follow. A review of decontamination techniques has been provided elsewhere (References 13, 14, 17, 21, 22).

Syrup of Ipecac

Alkaloids obtained from the root of the *Cephaelis acuminate* or *ipecacuanha* plant activate the chemoreceptor trigger zone and act directly on the small intestine to induce vomiting (Reference 14). Administration of SOI has been shown to provide removal of drugs in both volunteers and overdosed patients (References 23–25). However, the percentage returned can be highly variable, and it wanes rapidly enough that recovery is likely to be insignificant by the time most patients receive SOI (Reference 26). An analysis of poison exposure data in children found that the use of SOI had no impact on either emergency department referral or outcomes (Reference 15). In addition, although the administration of SOI has been proven safe, rare serious adverse events can occur, and the potential for abuse exists, which can lead to myopathy, cardiomyopathy, and death with chronic use (References 27, 28). Because of this lack of impact on clinical outcomes and because, in many instances, ingestion by children results in no to minimal harm, SOI is no longer recommended for routine use (Reference 12). In the rare cases when SOI is considered, dosing is as follows: age 6–12 months, 5–10 mL; 1–12 years, 15 mL; adolescents and adults, 30 mL. Water may be offered after administration (Reference 14).

Gastric Lavage

Because of a lack of evidence of effectiveness and a relatively high complication rate, routine use of gastric lavage is not recommended (Reference 17). Data made available since the first publication of the consensus statement in 1997 have not altered that recommendation (References 29–31). In addition, there are serious risks including delaying definitive antidote administration, aspiration, mechanical injury, hyponatremia, hypothermia, and death (References 18, 22). In the rare instance that a risk-benefit analysis predicts potential benefit to gastric lavage, it is recommended that it be performed within an hour of ingestion and continued until returns are clear (Reference 17). However, clear returns do not exclude a significant ingestion or guarantee that all toxin has been removed. In addition, the possibility remains that a significant amount of drug is still available in the stomach several hours after ingestion, though lavage appears variably effective at best in these situations (References 32, 33).

Activated Charcoal

Activated charcoal is produced when substances high in carbon content (e.g., wood, peat) are heated and then treated with steam or carbon dioxide (Reference 13). This results in a high surface area that allows the adsorption of other substances. Activated charcoal remains the only commonly used method of gastric decontamination (Reference 2). Current recommendations call for considering the use of AC within 1 hour in patients with a potentially toxic ingestion (Reference 13). Data available since the 2005 consensus statement have supported this recommendation, suggesting that AC provides minimal if any benefit in poisoned patients and decreased efficacy 1–2 hours postingestion (References 34–37). However, other data suggest AC can be effective in preventing sequelae and hastening the elimination of toxin, even when given after 1 hour postingestion (References 38, 39).

Administration of AC to children in the home has been investigated in an effort to increase efficacy by earlier administration. It appears it is feasible for parents and caregivers to administer safely. However, this has not been consistently shown, and considering risk of too-frequent and inappropriate use, home administration is not recommended (References 12, 40, 41).

An AC-to-drug ratio of 10:1 is recommended. However, in most poisonings, the exact amount of drug ingested is unknown. Thus, it is suggested that adults receive 25–100 g (providing adsorption of around 2.5–10 g of drug) and that children receive 0.5–2 g/kg, or as much as can be tolerated (Reference 11). If the 10:1 ratio is unlikely to be achieved with a maximally tolerated single dose, multidose AC or other decontamination methods should be considered. Activated charcoal is a relatively safe intervention. Vomiting is the most likely complication in children, and vomiting before administration and nasogastric tube placement appears to increase the risk (Reference 20). Complications that are more serious, such as aspiration or bowel perforation, are much less common (References 13, 19).

Multiple-dose activated charcoal (MDAC) is defined as the administration of more than two sequential doses (Reference 42). Multiple doses provide benefit by preventing prolonged absorption or enterohepatic recirculation ("gastric dialysis") (References 43, 44). Drugs are present in the gastrointestinal tract not only because of ingestion, but also because of diffusion from the circulation back into the lumen of the gut. Drug concentrations in the circulation decline as metabolism and elimination occur, limiting the amount of drug that can diffuse back into the gut lumen. Administration of AC causes enhanced elimination of drug from the gut through adsorption and elimination in the stool. This results in a "sink," described by an increased drug gradient between the circulation and the gut lumen, allowing more drug to diffuse into the gut lumen, where it can be adsorbed by AC and eliminated. Repeated administration of AC enhances this process of gastric dialysis of certain drugs.

There are scant clinical outcome data to support the use of MDAC. However, there may be benefit in treating poisoning from agents to which children are exposed, including phenobarbital, carbamazepine, theophylline,

Table 4. Gastric Decontamination Methods (References 13–21)

Method	Mechanism	Indications	Contraindications	Adverse Effects	Comments
Syrup of ipecac	Alkaloids emetine and cephaline activate vomiting center in CRTZ and act directly in small intestine; vomiting usually occurs within 20 minutes	Ingestions presenting within 1 hour with expected airway patency and normal mental status 1 hour after administration	Caustic, hydrocarbon, battery, and sharp ingestions; ingestions expected to cause altered level of consciousness; significant prior vomiting; nontoxic ingestion	Persistent vomiting, sedation, vagal bradycardia, delay of definitive therapy, esophageal tear, pneumomediastinum (rare); relatively safe when used appropriately	May be most useful in large ingestions when/where AC not effective; early administration can result in significant returns, so availability in remote areas may be prudent; alternative cause should be suspected for vomiting > 2 hours after dose; use requires expectation of normal state of consciousness at least 1 hour after use; because of very limited clinical utility, reported use has decreased from 15% of exposures in 1985 to less than 0.03% of exposures in 2009
Gastric lavage	Gastric intubation with 22–28 Fr orogastric tube; patient placed in left lateral decubitus position; 10–15 mL of warm saline per kilogram administered and removed	Life-threatening ingestions presenting within 1 hour; risk-benefit assessment recommended	Hydrocarbon, caustic ingestions, unprotected airway, patient at risk of hemorrhage or perforation	Airway or esophageal injury, hypoxia, electrolyte and core temperature disturbances	Saline should be used in children to prevent electrolyte disturbances; process is physically and emotionally traumatic in children; airway protection is imperative because children often vomit during tube placement; tube size in small children is prohibitive, contributing to decline in use of this method
Activated charcoal	Reversible adsorption, possibly by hydrogen/ionic binding, van der Waals forces; high surface area maximizes adsorption	Potentially toxic ingestions when administered within 1 hour	Caustic, alcohol, metal, hydrocarbon ingestions; ileus, gastric, or intestinal perforation	Vomiting (from AC or NG tube placement) more common if coadministered with sorbitol; aspiration, bowel injury rare but severe	Unpalatable because of thick, gritty texture; if not premixed, combine with water or cola in a 1:8 ratio, disguise preparation, or administer by NG tube; airway must be protected; sorbitol should only be given with initial dose, if at all
Whole bowel irrigation	Polyethylene glycol and electrolyte solution flushes gastrointestinal tract	Very large ingestions when poor outcome is likely; SR or EC product poisonings, particularly in those presenting > 2 hours after ingestion; ingestions when AC is ineffective; removal of drug packets from gastrointestinal tract	Ileus, gastrointestinal hemorrhage, perforation, obstruction, uncontrolled vomiting, diarrhea with volume depletion or hemodynamic instability	Vomiting, bloating, cramping; colonic perforation, esophageal tears, aspiration rare	Balanced solution prevents electrolyte imbalances; continue until effluent clear or no opacities on radiograph if present before therapy

AC = activated charcoal; CRTZ = chemoreceptor trigger zone; EC = enteric coated; Fr = French; NG = nasogastric; SR = sustained release.

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amitriptyline, digoxin, and phenytoin (Reference 42). Publications since the 1999 American Academy of Clinical Toxicology position statement have shown mixed efficacy (References 34, 35, 39, 45). However, in large overdoses when protein binding is exceeded, enterohepatic recirculation occurs, or absorption or first-pass metabolism is slowed, MDAC may be clinically useful (Reference 11). If MDAC is employed, a standard loading dose should be given, followed by 0.5 g/kg every 4–6 hours for up to 24 hours or until the patient's condition has improved or drug serum concentrations are no longer in the toxic range (References 42, 46).

An important consideration is the potential for AC to adsorb not only the ingested poison, but also other agents used in managing the poisoning. For example, AC has been shown to cause a statistically significant decrease in the absorption of *N*-acetylcysteine (NAC) when administered concurrently. Clinically, this does not appear to be significant. However, the interaction can be minimized by separating the administration of the two agents by 1–2 hours or using the intravenous NAC preparation (Reference 47).

Whole Bowel Irrigation

Whole bowel irrigation (WBI) is performed using a polyethylene glycol and electrolyte solution to essentially flush out the gastrointestinal tract. This preparation prevents electrolyte abnormalities associated with older cathartics such as sodium phosphate (Reference 48). Use should be considered in overdoses of sustained-release or enteric-coated drugs, iron, or other metal ingestions; in patients acting as carriers of illicit drug packages; and in those with mushroom or other plant ingestions (Reference 21). Since the publication of a position statement on WBI from the American Academy of Clinical Toxicology, there has been little published evidence of efficacy. Some investigations have used WBI in overdoses when it would not be considered clinically (e.g., acetaminophen), and use of WBI could potentially decrease the adsorptive capacity of AC (References 11, 49).

The solution can be given orally, but in children, it is often easier to administer by nasogastric tube. Small children should receive 0.5 L/hour, whereas older children and adolescents should receive 1.5–2 L/hour. The older patient should sit on a toilet, whereas diapers are required in small children and infants. Administration for 4–6 hours is usually necessary to achieve a clear effluent (Reference 21). Several products are available for WBI, including GoLYTELY, NuLYTELY, and Colyte, and these may be flavored for palatability. However, MiraLAX, commonly used for managing constipation in children, should not be used for WBI because it contains no electrolytes, increasing the risk of electrolyte abnormalities (Reference 48).

Review of Management of Select Poisonings

A review of the management of multiple toxic exposures is beyond the scope of this chapter. However, poisonings occur that, although perhaps not the most common statistically, have several aspects of management unique to the pediatric population. Analgesics, particularly acetaminophen, are quite commonly ingested by children, and the toxic dose differs from that of adults on a kilogram basis. Antidote therapy for toxic alcohol exposure has changed in recent years, and additional pediatric data have guided the management of these exposures in children. Management of snakebites in children is similar to that in adults, but many issues need to be considered when administering antivenin to children. Care of children who have ingested or been exposed to these three toxins is discussed in the following paragraphs.

Acetaminophen

When dosed therapeutically, acetaminophen has a very good safety profile in children (References 50–52). Acetaminophen is also widely available in many dosage forms and drug combinations. Therefore, it is not surprising that in 2009, there were almost 50,000 toxic exposures to acetaminophen in children younger than 6 years. Overall, acetaminophen was the fourth most common toxin associated with death, involved in more than 10% of adult poisoning fatalities. Nevertheless, outcomes in children were good, and no fatalities were reported in anyone younger than 17 years (Reference 2). However, acetaminophen is the most commonly identified cause of acute liver failure in children (Reference 53).

After absorption, around 90% of an acetaminophen dose is glucuronidated and sulfated. These metabolites, and a small percentage of unchanged drug, are eliminated in the urine. The rest is metabolized by the cytochrome P450 (CYP) system to a toxic metabolite, *N*-acetyl-*p*-benzoquinonimine (NAPQI). This metabolite is rapidly toxic to liver cells, but natural stores of glutathione conjugate it, and this complex is eliminated in the urine. In an overdose, glutathione stores become depleted, NAPQI is no longer detoxified, and direct liver damage results (Reference 47). In untreated patients, acetaminophen toxicity typically progresses through the following four stages. After ingestion, gastrointestinal symptoms such as nausea and vomiting predominate, though patients may be asymptomatic. No liver damage has occurred yet. Stage 2 may occur as early as 12 hours in large overdoses, but typically by 24–36 hours postingestion, there is evidence of acetaminophen-induced hepatotoxicity, defined as aspartate aminotransferase

concentrations greater than 1000 IU/L. Maximal liver damage occurs in stage 3, 3–4 days postingestion. Patients may experience fulminant hepatic failure, encephalopathy, coma, and hemorrhage. Alanine aminotransferase and aspartate aminotransferase may exceed 10,000 IU/L, and elevations in PT (prothrombin time) and INR (international normalized ratio) are possible. Renal toxicity can occur with or without the presence of hepatic toxicity, but it more often occurs shortly afterward. The incidence of renal toxicity is unclear and is thought to be a rare event; however, it has been reported to be as high as 8.9% (References 47, 54, 55). Death occurs in 3–5 days because of multiple organ failure. Survival to stage 4 should result in recovery of liver function, with laboratory values returning to normal within 1 month (Reference 47). Of note, although published data suggest a wide variation in outcomes, there is significant risk of fulminant or fatal hepatotoxicity in patients with acetaminophen poisoning who do not receive treatment. However, even without treatment, fatality rates likely do not exceed 20% (Reference 56).

The decision to initiate therapy for acetaminophen poisoning is dictated by the amount ingested. Acute ingestions of 7.5–15 g in adults or 150 mg/kg in children have conventionally been considered toxic. However, there are no data in children to support this, and it is unlikely that significant liver toxicity would occur with doses less than 200 mg/kg (References 57–59). With the recent FDA labeling of intravenous acetaminophen in the United States, frequent 10-fold dosing errors have been documented in countries where it has been available for several years, and toxicity has been reported in children with intravenous acetaminophen in doses well under 200 mg/kg (References 60, 61). It is suggested that in suspected dosing errors (or a single dose greater than 60 mg/kg) with this product, strong consideration be given to antidote therapy while a toxicologic assessment can be completed (Reference 60). Even though acetaminophen is absorbed relatively quickly and an effective antidote exists, gastric decontamination can be considered if the patient presents early after ingestion. Syrup of ipecac and gastric lavage are typically not indicated. Activated charcoal can be given within 1–2 hours after ingestion and may help keep serum concentrations below the treatment line of the Rumack-Matthew nomogram (Reference 47). The Rumack-Matthew nomogram (Figure 1) permits a single acetaminophen concentration obtained at least 4 hours after ingestion to be used to assess the risk of hepatotoxicity (Reference 47). The treatment line, at 25% below the dotted line in the figure, is used to justify antidote therapy. If the serum concentration is on or above the treatment line between 4 and 24 hours, therapy is initiated. Of note, the Rumack-Matthew nomogram is validated only for use in single, acute, oral ingestions. Toxicity from the intravenous preparation or from chronic exposure cannot be reliably assessed by the nomogram. The toxicity risk of the extended-release acetaminophen product can be reliably assessed because peak acetaminophen concentrations occur in a time frame similar to that of immediate-release products. However, if the initial serum concentration is below the treatment line, it is prudent to repeat a measurement at about 8 hours after ingestion to confirm risk assessment because a small percentage of patients may cross above the treatment line.

Antidote therapy is provided with NAC. It can prevent hepatotoxicity by providing a substrate for glutathione production and binding NAPQI directly, and it can decrease present hepatotoxicity by free radical scavenging and antioxidant effects (Reference 62). *N*-acetylcysteine may be administered orally or intravenously. Some authors have suggested that the oral route be used in patients presenting within 8–10 hours of ingestion and that intravenous NAC be administered when presenting 10 hours or more after ingestion (Reference 63), whereas others have suggested the opposite is true (References 64, 65). However, in most instances, it appears efficacy should be equivalent, particularly when given within 8 hours (References 61, 64). One apparent advantage to intravenous administration is the 21-hour infusion time (150 mg/kg over 1 hour; then 50 mg/kg over 4 hours; then 100 mg/kg over 16 hours) compared with the 72-hour oral regimen (140 mg/kg × 1; then 70 mg/kg every 4 hours × 17 doses). This opportunity for decreased length of hospital stay offsets the higher cost of the intravenous NAC product. However, several authors have found that shorter courses of the oral product may be as effective as the traditional 72-hour regimen (References 66–68). Use of these shorter regimens would make the oral route more cost-effective.

Both formulations have proven safe in acetaminophen overdose. The most common adverse events with oral administration are nausea, vomiting, and diarrhea, whereas anaphylactoid reactions (rarely serious) are more common with the intravenous preparation (References 62, 65, 69). An additional consideration with standard dilution of the intravenous product is the potential for excess free water administration, resulting in hyponatremia and seizures. In younger patients, more concentrated solutions should be administered (References 70, 71). For example, in adults, the three infusions are given in volumes of 200 mL, 500 mL, and 1000 mL, respectively, resulting in

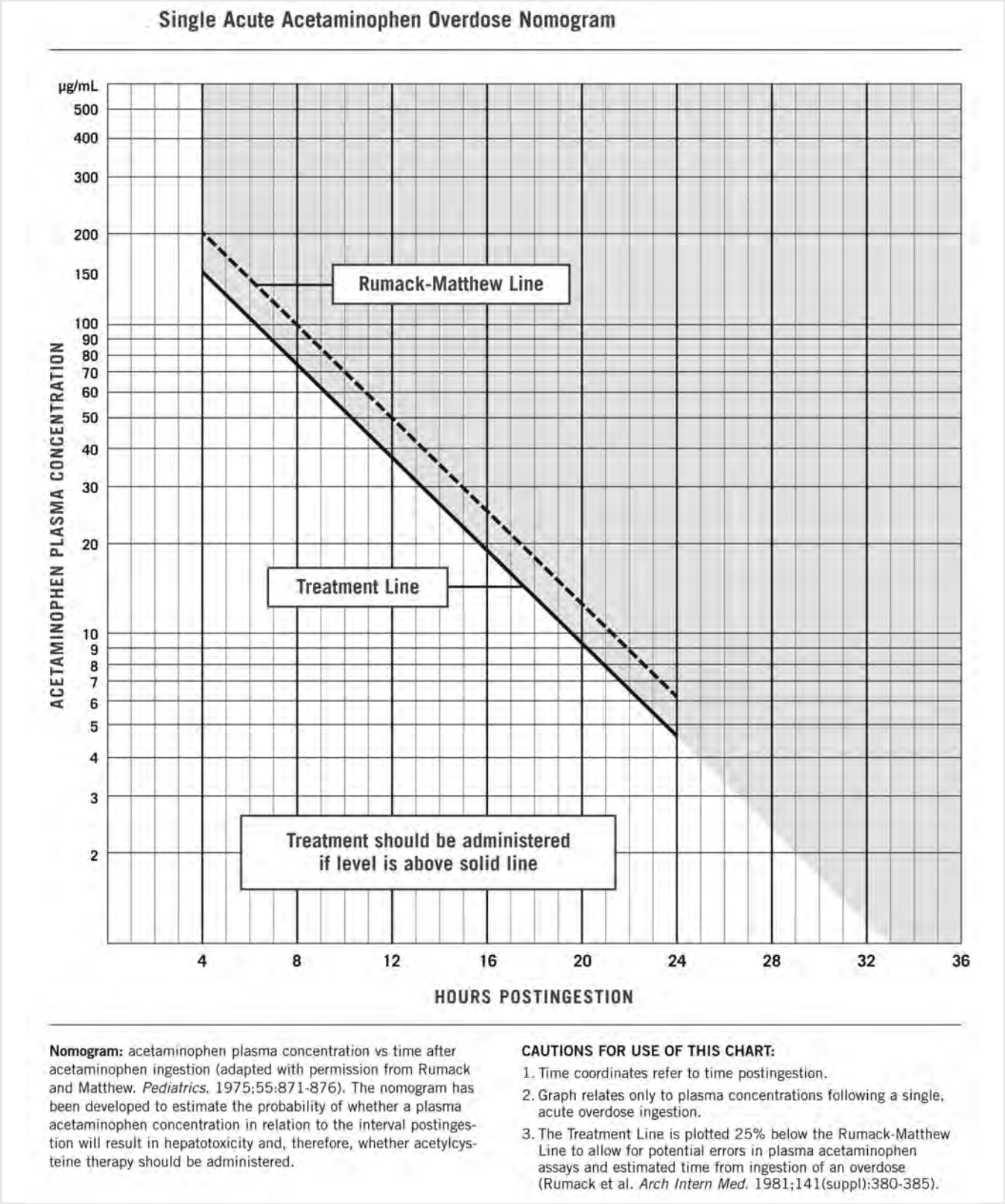


Figure 1. Rumack-Matthew nomogram.

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concentrations ranging from about 40 mg/mL to less than 5 mg/mL. To prevent the development of hyponatremia in children, the product should be diluted to a concentration of 40 mg/mL for all three phases.

Ethylene Glycol and Methanol

Ethylene glycol and methanol pose serious risks to children because they can be found in the home in several different products, and very small amounts can be deadly in small children (References 72, 73). Ethylene glycol is the primary ingredient in engine coolant, and the sweet taste increases the likelihood of significant ingestion in unsuspecting children and pets. Methanol can be found in solvents, antifreeze, fuels, and photocopying fluid, but it is most often encountered in windshield washer fluid (References 74, 75). In 2009, there were 4852 single exposures to ethylene glycol (10% in children younger than 6 years), and more than 1700 (23% in children younger than 6 years) single exposures to methanol were reported. There were 20 fatalities, but no fatalities were reported in children (Reference 2).

Aside from central nervous system depression, ethylene glycol and methanol are not in themselves responsible for the toxic effects. In the first several hours after exposure, patients with ethylene glycol ingestions may present with decreased mental status, ataxia, slurred speech, and, in larger ingestions, coma. During this time, ethylene glycol is metabolized by alcohol dehydrogenase to glycoaldehyde and then by aldehyde dehydrogenase to glycolic acid (most responsible for metabolic acidosis), which is further metabolized to glyoxylic acid and oxalic acid (References 74, 75). In the 12–24 hours after ingestion, these metabolites result in cardiopulmonary compromise such as respiratory distress, tachycardia, congestive heart failure, and cardiovascular collapse. From 1 to 3 days after ingestion, nephrotoxicity predominates because of calcium precipitation of oxalic acid in renal tubules. Significant hypocalcemia leading to tetany or changes in electrocardiogram may occur as well (References 73–75). Methanol is metabolized by alcohol dehydrogenase to formaldehyde and then by aldehyde dehydrogenase to formic acid, which is most responsible for metabolic acidosis (Reference 74). Symptoms in the first 12–24 hours after ingestion include depressed mental status and tachypnea. The accumulation of formic acid can result in hallmark visual disturbances such as blurriness ("snow field vision") and blindness, which can be permanent (Reference 76). Other signs and symptoms can include gastrointestinal distress, headache, shock, and seizures (References 73–75).

Initial management includes supportive care and efforts to resolve metabolic acidosis. Laboratory evaluation should include serum chemistries, lactate, and ionized calcium. Serum ethylene glycol or methanol concentrations should be obtained if available, though at many institutions, this measurement must be sent to a reference laboratory, limiting clinical utility (though controversial, serum concentrations of ethylene glycol and methanol above 25 mg/dL are considered toxic). Anion gap and osmolar gap calculations can be completed to assist in diagnosing exposures. However, a normal gap does not rule out clinically significant poisoning (Reference 74). Gastric decontamination is, in a vast majority of cases, not recommended in toxic alcohol ingestions. Syrup of ipecac is not indicated because of central nervous system depression, and AC does not effectively adsorb alcohols (Reference 46). It may be useful to insert a nasogastric tube to aspirate stomach contents in intubated patients in some instances, particularly in large ingestions when absorption may be delayed (Reference 74). Other potentially helpful supportive measures include administering folic acid in methanol poisoning and giving pyridoxine and thiamine in ethylene glycol poisoning to enhance the elimination of toxic metabolites (References 73–75, 77–79). Folic acid or folinic acid can be given intravenously at 1 mg/kg (maximal dose 50 mg) every 4–6 hours for 24 hours or until methanol and formic acid have been eliminated. Pyridoxine and thiamine can be given intravenously in doses of 100 mg/day until ethylene glycol is eliminated. Data regarding the efficacy of these adjunctive therapies are limited, but the risk-benefit ratio is sufficiently low that they should be administered in all patients.

Definitive therapy is aimed at preventing the metabolism of ethylene glycol or methanol to its more toxic metabolites. Historically, the only available option has been ethanol. Ethanol has an affinity for alcohol dehydrogenase several times that of ethylene glycol and methanol (Reference 80). This prevents the accumulation of toxic metabolites and allows renal and pulmonary elimination of the parent alcohols. Ethanol has been used safely in children, and it can be given intravenously or orally, with the goal of maintaining serum concentrations of 100–150 mg/dL. This can typically be achieved by administering an intravenous loading dose of 8 mL/kg of 10% ethanol over 1 hour, followed by an infusion of 0.8 mL/kg/hour. Frequent serum ethanol concentrations will need to be obtained because of the variability in patient pharmacokinetics (Reference 80). However, there are several disadvantages. Administration of intravenous ethanol requires a central venous catheter because of the high osmolarity. Ethanol can contribute to central nervous system and respiratory depression, and it may cause hypothermia, hypoglycemia, and hyponatremia,

necessitating intensive care monitoring (References 80, 81). In addition, repeated serum ethanol concentrations are required because metabolic rates vary significantly, and though ethanol can be used safely in children, the potential for significant adverse reactions exists (References 75, 82). If used, ethanol should be continued until ethylene glycol or methanol concentrations are below 25 mg/dL.

Fomepizole (4-methylpyrazole) was made available for use in the United States in 1997. It is a competitive alcohol dehydrogenase inhibitor with an affinity several thousand times that of ethanol for alcohol dehydrogenase (References 72, 83). Fomepizole is effective in the management of both ethylene glycol and methanol ingestions (References 81, 82, 84, 85). Several advantages of fomepizole over ethanol are as follows: no alteration in level of consciousness; no effect on blood glucose or electrolytes; no requirement of central venous access; and no requirement for intensive care if the patient is stable. Patients should receive a loading dose of 15 mg/kg, followed by 10 mg/kg every 12 hours for four doses, and then 15 mg/kg every 12 hours until serum ethylene glycol or methanol concentrations are below 25 mg/dL (Reference 83). A course of fomepizole costs about 4 times that of a course of ethanol. However, the lack of need for intensive care monitoring likely makes fomepizole more cost-effective than ethanol, and this drug has become first-line therapy in toxic alcohol ingestions (References 72, 81, 86, 87). The need for hemodialysis as a treatment modality has decreased significantly since fomepizole became available. However, hemodialysis still may be necessary in patients with severe acidosis, end-organ toxicity, serum concentrations of ethylene glycol or methanol above 50 mg/dL, large ingestions, or late presentation, in whom significant metabolite buildup has occurred and inhibition of alcohol dehydrogenase would be ineffective (References 73, 74).

Crotaline Envenomations

Crotaline snakes (Viperidae, subfamily Crotalinae) include the rattlesnake, copperhead, and cottonmouth. These snakes are also referred to as pit vipers because they have a heat-sensing pit posterior to the nostrils. Additional features that distinguish the Crotaline snakes from nonvenomous North American snakes include a triangle-shaped head, visible fangs, and elliptical pupils (References 88, 89). It is estimated that 8000 snakebites occur annually in the United States (Reference 88). In 2009, 3381 envenomations caused by crotaline snakes were reported; 789 occurred in children younger than 19 years. More than 1200 of these envenomations were from rattlesnakes, of which three fatalities were reported—none in children (Reference 2).

Crotaline venom contains a large number of substances, including enzymes, peptides, amino acids, metallic ions, lipids, and carbohydrates. These components are present in varying quantities and potencies, depending on the age and nutritional status of the snake, geographic region, season, and climate. Once injected, venom is absorbed through lymphatic and venous drainage. The venom then results in local tissue damage, including capillary endothelial destruction, leading to leakage of plasma and red blood cells into tissues, causing significant edema, erythema, and ecchymosis (References 89, 90). After local tissue destruction, hematologic toxicity is the most prominent effect of venom and includes coagulopathy, hemolysis, and thrombocytopenia (References 88, 91). Prothrombin times may be extremely high, even early after a bite, and platelet counts may be very low. Although local and hematologic effects predominate, respiratory, cardiovascular, and neurologic effects may manifest as well. Symptom severity caused by envenomation is related to the amount of venom injected, which depends on fang penetration, the amount of time the snake is allowed to bite, and the length of time since the snake last expended venom. About one-fourth of bites are "dry," meaning no venom is released by the snake (References 89, 90). The severity of the envenomation can be assessed by one of several scoring systems (References 92, 93). In general, scoring is as follows. (1) With minimal envenomation, there is local pain and swelling only, with no systemic manifestations. (2) With moderate envenomation, there is local tissue involvement in addition to non–life-threatening systemic signs and symptoms with possible coagulation abnormalities, but no evidence of bleeding. (3) With severe envenomation, there is local tissue damage in addition to altered mental status, hypotension, tachycardia, and coagulation abnormalities with severe bleeding or possible severe bleeding (References 72, 91).

After envenomation, symptoms usually occur within several minutes, if not immediately. Patient presentation includes fear, anxiety, intense pain (more than would be expected from the size of the wound), weakness, and dizziness. Those with more severe envenomations can present with altered mental status, tachycardia, visual disturbances, and a metallic taste (Reference 89). Prehospital supportive care involves first moving the victim away from the snake and then transporting the victim to a health care facility as soon as possible. It is not recommended to search for or to try to capture or kill the snake. Instead, the focus should be on calming the patient and keeping him or her warm, and the affected limb should be immobilized and positioned below heart level. Tight-fitting clothing and jewelry such as wedding bands should be removed. Application of ice or tourniquets, incision

or excision of the wound, or use of suction devices is highly discouraged (References 89, 90). Emergency department management involves first ensuring airway, breathing, and circulation. A detailed history of the event, as well as any comorbid conditions and allergy history, should be obtained. A detailed physical examination should be performed, and the initial laboratory evaluation should include a complete blood cell count, platelet count, coagulation studies, serum electrolytes, and urinalysis (References 89, 90).

Definitive therapy for crotaline envenomation was formerly provided with antivenin (Crotalidae) polyvalent, an equine-derived whole immune globulin antibody formulation. This preparation, in use since the 1950s, proved effective and significantly reduced mortality caused by Crotalidae envenomations. However, one-fourth to one-half of patients receiving antivenin (Crotalidae) polyvalent had an acute reaction, including vomiting, rash, dyspnea, cyanosis, and anaphylaxis, and the rate of serum sickness ranged from almost 20% to more than 80% of patients (Reference 94). Antivenin (Crotalidae) polyvalent is no longer manufactured.

In 2000, Crotalidae polyvalent immune Fab antivenom (FabAV) was approved for use. This product is indicated for treating the victims of envenomation by North American crotaline snakes. It is a monovalent ovine Fab derived by inoculating sheep with the venom of the western diamondback, eastern diamondback, Mojave, or cottonmouth rattlesnake, though case reports suggest efficacy against several other types of snake as well (References 94–98). The final product is a lyophilized mixture of antibodies from all four antivenins (Reference 99). Crotalidae polyvalent immune Fab antivenom binds venom that has reached the intravascular space, and the complex is eliminated renally. The Fab fragments are small enough to reach interstitial spaces, preventing further tissue damage (Reference 88).

The severity of the envenomation determines the FabAV dose. Of note, dosing is not based on the size of the child. Crotalidae polyvalent immune Fab antivenom works by neutralizing a specific amount of venom; thus, the dosing recommendations apply to both children and adults. From 4 to 6 vials, each containing 1 g of total protein, should be administered over 1 hour in 250 mL of normal saline. If the venom has been neutralized (no progression of local tissue damage; normalization of systemic signs and symptoms and coagulation disturbances), a maintenance regimen of 2 vials every 6 hours for up to 18 hours should be administered. If, after 1 hour, control of the envenomation is not achieved, an additional dose of 4–6 vials should be administered; this regimen should be repeated until signs and symptoms have ceased to progress. Ideally, administration should occur within 4–6 hours of the bite (Reference 99).

Although a relatively small amount of literature describes the use of FabAV in children, it has been shown to be effective in managing pediatric snakebite victims (References 100–103). Most patients achieve initial control with the first dose. Still, delayed complications, including recurrent coagulopathy, have been reported in children despite initial therapeutic success (References 104, 105). Follow-up within 1 week after discharge seems prudent. Crotalidae polyvalent immune Fab antivenom appears to be well tolerated in children. Overall, adverse events are less frequent with FabAV than with antivenin (Crotalidae) polyvalent because only about 10% to 20% of patients experience acute and delayed reactions (Reference 94). However, in children, adverse event rates appear to be lower (Reference 106). The infusion rate may contribute to adverse events, necessitating dose titration. It is recommended that the initial infusion be given at 25 mL/hour for the first 10 minutes. This may be increased as tolerated up to 250 mL/hour, though the infusion should be given over at least 1 hour (References 92, 99). Pretreatment with diphenhydramine may be considered, and epinephrine, albuterol, and corticosteroids should be available during an acute reaction.

An additional administration concern in children is volume overload, particularly in infants or in large envenomations requiring several doses of FabAV. Although there are no published reports of this occurring, caution should be taken in children with pulmonary, cardiac, or renal conditions. Some institutions provide the initial 4- to 6-vial dose in 2-vial increments in 100 mL of normal saline, which may guard against potential volume overload in small children (Reference 92). Such incremental dosing may also prevent waste if it is determined the entire dose is not necessary. This is important because acquisition costs are about $1000 per vial or gram (References 92, 103). Time to reconstitute vials must be considered as well. The package insert recommends diluting vials in 10 mL of sterile water for injection before final preparation. This can take several minutes; thus, early notification of the pharmacy department is important in providing rapid administration. Some data suggest that diluting each vial in 25 mL of sterile water for injection and then hand mixing will result in significant decreases in reconstitution times (Reference 107).

Management of Other Common Pediatric Exposures

As noted, most pediatric toxic exposures result in minimal to no effects. Many calls to the poison center involve exposures to essentially harmless substances, such as cosmetics, toothpaste, and crayons (though it is of note that colognes and perfumes contain significant amounts of ethanol and can result in significant toxicity). Other common

exposures like household cleaners, foreign bodies (batteries), and cough and cold preparations, though usually not serious, can result in significant toxicity. A discussion of these exposures is provided in the following section.

Household Cleaner and Caustic Exposure

In 2009, household cleaning substances were the third most commonly reported exposure in children younger than 6 years; in fact, these substances are the third most commonly reported exposure overall (Reference 2). Yet the number of children younger than 6 years requiring emergency department management of injuries from household product exposure has decreased by almost 50% in the past 15 years (Reference 108). Examples of household cleaner products encountered include bleaches, detergents, and soaps. Examples of caustics include acids and alkalis found in products such as toilet, drain, and oven cleaners.

In most pediatric exposures to these substances, there is no intent to self-harm, so ingestion or exposure quantities are likely to be limited, minimizing the risk of an adverse outcome. However, even with small to moderate exposure, symptoms may be observed. Ingestion of detergents and soaps may result in drooling, nausea, vomiting, gastric pain, and respiratory distress, if aspirated. Some products, if sufficiently alkaline, may result in esophageal injury, whereas strong acids are more likely to cause gastric injury (Reference 109). Bleach exposure would present in similar fashion, though the risk of esophageal injury is low with household-strength preparations (usually 3% sodium hypochlorite). Medical management in most children involves supportive care. Fluids may be offered to the asymptomatic or mildly symptomatic child, and observation is typically sufficient (Reference 110). Vomiting should not be induced (Reference 111). Neutralization, offering acidic beverages in alkaline ingestions and alkaline beverages in acidic ingestions, should not be performed. After large ingestions or ingestions of highly concentrated substances, endoscopy, surgical, and further medical intervention may be necessary (Reference 112).

Foreign Body Ingestion

Foreign body ingestion can include coins, toys, and ornaments. Unless the object is composed of a significantly toxic agent (e.g., lead) or is aspirated, management usually consists of observation, though manual removal may be necessary in esophageal impaction. However, disc batteries, because of their composition, present further risk. In 2009, more than 3000 disc battery exposures were reported (Reference 2). Most batteries are obtained by children from products such as games, hearing aids, watches, calculators, and remote controls (Reference 113).

In most cases of battery ingestion, the disc passes the esophagus into the stomach. From there, it usually passes through the intestinal tract within 1–2 weeks and results in no symptoms. However, the battery may become lodged in the esophagus and result in serious and life-threatening complications such as burns, perforations, and fistulae (References 114, 115). This damage is caused by alkaline electrolyte leakage from the battery, pressure necrosis, and external current generation when the battery comes in contact with tissue (References 113, 116). Signs and symptoms include vomiting, diarrhea, abdominal pain, fever, refusal to eat or drink, and dysphagia (Reference 115). When impaction occurs, it should be removed immediately. Of note, in addition to the esophagus, one may encounter children with batteries lodged in the nose, ears, or other body cavities, and it is important in these cases to remove the battery as soon as possible as well. The larger the battery, the more likely impaction will occur. Battery diameter can range from just more than 5 mm to 25 mm, and children ingesting batteries of 20 mm in diameter or more are more likely to develop significant complications (Reference 113). In addition to the national poison hotline, a national battery ingestion hotline [(202) 625-3333] exists to provide guidance in managing an ingestion. The following Web site at the National Capital Poison Center provides further information: www.poison.org/battery.

Cough and Cold Preparations

There is little, if any, evidence to support the use of cough and cold preparations in children for the management of cold symptoms (Reference 117). In fact, evidence exists that these preparations are associated with fatalities and apparent life-threatening events (References 118–120). Pseudoephedrine is most commonly associated with fatalities. In most instances of death reported in these publications, the drug was given at home and at higher-than-recommended doses. Often, the child was given several drugs with similar ingredients, the dose measurement was inaccurate, an adult formulation was used, or the child was given doses by multiple caregivers.

In 2007, an FDA advisory panel recommended that these drugs be avoided in children younger than 6 years, though the FDA still recommends that they be avoided in children younger than 2 years. However, partly because of the advisory panel recommendation, manufacturers have voluntarily withdrawn cough and cold products intended for children younger than 2 years, and the Consumer Healthcare Products Association has updated labels to state that use should be avoided in children younger than 4 years.

Management of toxicity from these products is primarily supportive, as discussed earlier. Gastric decontamination, primarily AC, can be used if the patient presents early and the airway is protected. Symptomatic therapy may be necessary, including the management of hypertension, arrhythmias, and seizures.

Conclusions

Although most toxic exposures occur in the pediatric population, serious or fatal outcomes are quite rare. The American Association of Poison Control Centers and the National Poison Data System provide health care professionals with information that can shape public health and educational efforts. Any pharmacist or health care professional involved in the care of children should be familiar with this resource.

Medical management of the poisoned child can be similar to that of an adult patient in many respects. However, obtaining an accurate history, particularly the amount ingested, can be difficult, making physical and laboratory examination and patient presentation key to effective management. Knowledge of and familiarity with available resources, especially the poison control center, will help clinicians of any experience level provide the best care for pediatric patients who have been poisoned.

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CHAPTER 8

Pediatric Dermatology

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Learning Objectives

1. Provide general recommendations for skin care in infants and children.
2. Identify topical products that should typically be avoided in infants and children.
3. Recommend pharmacologic and nonpharmacologic treatment for diaper dermatitis.
4. Recommend treatment for seborrheic dermatitis of the newborn.
5. Recommend pharmacologic and nonpharmacologic treatment for dermatophytic fungal infections in children.
6. Provide recommendations for the pharmacologic and nonpharmacologic treatment of atopic dermatitis in children.
7. Provide recommendations for the treatment of acne in adolescence.

Introduction to Skin Care for Infants and Children

Skin disorders in childhood are a common reason for health care use and self-care worldwide. Although some dermatologic conditions are unique to the pediatric population, many will continue into adulthood. However, the approach to therapy for skin disorders in children differs from that for adults because skin structure and function differ.

Skin is composed of the epidermis, dermis, and hypodermis. The outer layer of the epidermis, the stratum corneum, is responsible for preventing water loss and serves as the primary barrier to the penetration of medications and irritants. Children younger than 2 years are especially susceptible to skin damage, irritation, and systemic absorption of medications because they have a thinner and weaker stratum corneum and total skin layer (Reference 1). In addition, infants and children have an increased skin surface area-to-body weight ratio compared with adults. Preterm and term neonates are at increased risk because of an underdeveloped stratum corneum. Additional differences in the lipid component of the stratum corneum are observed until puberty, placing children at higher risk of bacterial and fungal skin infections (Reference 1).

General skin care for infants involves maintaining adequate hydration and avoiding products that may cause skin irritation. Gentle, fragrance-free soaps and emollients are recommended, with emollient application occurring after bathing. Certain products should be avoided that may cause irritant dermatitis or harmful systemic absorption. Table 1 includes a list of ingredients that should not be applied topically to children younger than 2 years and those with skin disorders, when possible (Reference 2).

Common dermatologic conditions in childhood include diaper dermatitis, atopic dermatitis, acne, warts, birthmarks, seborrheic dermatitis, and fungal or bacterial skin infections. This chapter will focus on common disorders requiring pharmacologic intervention. Treatment of bacterial skin infections will be discussed in detail in the Skin and Soft Tissue Infections chapter. For images of the conditions described, the Web site www.visualdx.com provides helpful examples.

Table 1. Topical Products to Avoid in Neonates and Infants (References 1, 2)

Products That May Cause Local Irritation	Products That May Cause Systemic Effects
Cod liver oil	Betamethasone
Hexachlorophene	DEET (> 10%)
Iodine	Hexachlorophene, resorcinol
Isopropyl alcohol (> 4%)	High-potency topical corticosteroids
Lanolin	Isopropyl alcohol
Neomycin	Mercury
Nickel	Methylene blue
Phenol	Neomycin
Propylene glycol	Povidine-iodine
Resorcinol	Salicylic acid
Thimerosal	Silver sulfadiazine
Topical antihistamines	Tacrolimus, pimecrolimus
	Topical anesthetics (e.g., benzocaine, prilocaine)
	Urea

DEET = *N,N*-diethyl-*m*-toluamide.

Diaper Dermatitis

Diaper dermatitis, commonly referred to as diaper rash, napkin rash, or nappy rash, is a non-specific term used to describe an inflammatory eruption of the skin in the diaper region. It is one of the most common skin disorders affecting infants and toddlers. The overall reported prevalence is variable at 7% to 50% (References 3, 4), but it is widely accepted that diaper dermatitis is underreported. Although thought of as occurring only in the pediatric population, it can occur in any individual requiring the use of diapers for a prolonged period.

Diaper dermatitis is usually the result of irritant contact dermatitis secondary to a combination of the following factors: presence of feces/urine, occlusive nature of the diaper, maceration of the skin, friction of the diaper, and alkaline pH of the skin (References 5–7). The occlusive nature of the diaper results in a moist environment, causing maceration of the skin and in turn decreasing the integrity of the barrier function of the skin. The decreased barrier function of the skin allows an increased permeability of irritants and microbial flora. Friction from movement, together with moisture in the diaper environment, further serves to physically break down the skin. The presence of feces (i.e., fecal enzymes), bile acid salts, and urine in the diaper also promotes the development of diaper dermatitis by acting as a direct irritant to the skin. In the presence of fecal urease, the urine is broken down to ammonia, contributing further to the basic pH of the diapered skin. The increase in pH subsequently results in an increased activity of the fecal enzymes (i.e., proteases and lipases) and further disruption of the barrier function of the skin. Secondary infection by either bacteria or yeast is thought to occur because of the decreased barrier function of the stratum corneum. *Candida albicans* may be present on the skin of infants with and without diaper dermatitis; however, extensive colonization can increase the severity of diaper dermatitis (Reference 8). *C. albicans* can be isolated in up to 80% of cases in which diaper dermatitis persists for 3 days or more (Reference 7).

Infants in cloth diapers are at greater risk of developing moderate or severe diaper dermatitis because cloth diapers do not possess the absorption capacity of disposable diapers and do not wick away the moisture as efficiently. In addition, by wicking away the urine, disposable diapers prevent the interaction of urine with fecal enzymes, decreasing the amount of ammonia produced. Studies have shown that formula-fed infants are more likely to develop moderate to severe diaper dermatitis compared with breastfed infants (Reference 5). Breastfed infants have lower stool pH and decreased levels of fecal enzymes. An additional risk factor associated with increased incidence of diaper dermatitis is the use of antibiotics and the development of antibiotic-associated diarrhea. A child with diarrhea is at increased risk of diaper dermatitis because of repeated exposure of the skin to feces (Reference 3).

Eruptions in the diaper area can be attributed to a variety of skin conditions. Differential diagnosis includes allergic contact dermatitis, seborrheic dermatitis, intertrigo, psoriasis, and infection (e.g., candidiasis, bullous impetigo, scabies, folliculitis). Simple diaper dermatitis presents as erythema and mild scaling on the skin that is in direct apposition with the diaper, sparing the skin folds. It may also present as shiny plaques or papules. Mild cases of diaper dermatitis are often self-limiting, with a mean duration of 2–3 days per episode (Reference 5). Progression to severe dermatitis (i.e., Jacquet diaper dermatitis) will present as severe ulceration in the diaper area. Secondary infection with *C. albicans* presents as an intense erythematous rash that is often described as beefy red in appearance. Unlike contact dermatitis, the rash is present in the skin folds and perianal skin. The erythematous patches and plaques are often accompanied by papules and pustules called satellite lesions. In most cases, a clinical diagnosis can be made on the basis of presentation; however, a diagnosis can be confirmed by culture or by performing a potassium hydroxide preparation of a scraping from the lesion.

Secondary bacterial infections are most commonly *Staphylococcus aureus* or group A *Streptococcus*. *S. aureus* often presents as bullous impetigo, with scattered vesicles that, on eruption, form superficial erosions with a honey-colored crust. Group A *Streptococcus* presents as perianal patchy erythema. If a bacterial cause is suspected, cultures may be obtained in an effort to provide targeted therapy for the specific organism. If the diaper rash remains after 1 month of vigilant treatment for irritant, bacterial, and yeast dermatitis, a further workup should be performed to rule out immunodeficiency, nutritional deficiency, metabolic disorders, or abuse/neglect (Reference 7).

Prevention of diaper dermatitis begins with educating the caregiver/parent on proper diaper hygiene. Removal of the diaper immediately after defecation is optimal, which prevents interaction of the urine and feces and subsequent increase in skin pH. The diaper area should be gently cleansed with water and a cotton cloth or commercial baby wipes to remove the irritants. If commercial products are used, products containing preservatives, fragrances, alcohol, or aloe should be avoided because they can cause further irritation. After cleansing, the diaper area should be patted dry. If feasible, daily diaper-free time should be implemented to allow exposure of the diaper area to the air. Use of superabsorbent disposable diapers will decrease the frequency and severity of diaper dermatitis. Empiric application of a barrier protectant as a preventive measure is not

necessary for all infants. If the infant is prone to develop diaper rash or is at increased risk, barrier protectants such as zinc oxide, petrolatum, or dimethicone may be used prophylactically. The barrier preparations protect the skin from irritants by coating it with a water-repellent barrier and serve to reduce friction by providing lubrication. The ointments and pastes provide better protection because they are not as easily removed. The product selected should have minimal ingredients and no other additives, which can lead to sensitization of the skin. Talcum powder and cornstarch have been used to absorb moisture, reduce friction, and prevent chafing in the diaper area. This practice should be discouraged because of the risk of aspiration of airborne particles and development of pneumonitis.

Treatment of diaper dermatitis involves both nonpharmacologic and pharmacologic therapy. Barrier protectants should be initiated at the first sign of erythema to prevent further irritation to the area. The barrier protectant should be applied with each diaper change. The nonpharmacologic measures recommended for the prevention of diaper dermatitis are also recommended for treating diaper dermatitis.

If a diaper rash remains or continues to progress after 3 days of treatment with barrier agents, a topical antifungal agent such as nystatin, miconazole, or clotrimazole should be initiated. The antifungal agent should be applied two times/day, as described in Table 2, until 1 week after the eruption has cleared (Reference 5). Most cases of yeast dermatitis resolve within 10 days of initiating antifungal therapy, but some cases may take up to 3 weeks to resolve (Reference 7). Some prescribers recommend application four times/day or with every diaper change if frequent diaper changes are required. Miconazole 2% and clotrimazole 1% are both available over the counter. Although not specifically labeled for candidal diaper dermatitis, nystatin ointment is available as a prescription product. An additional prescription product with specific labeling for candidal diaper dermatitis is a combination product of miconazole 0.25%, zinc oxide 15%, and white petrolatum. Other commercially available combination antifungal products, such as combination antifungal-corticosteroid products, should be avoided. These products, which contain high-potency corticosteroids, are contraindicated for use in the diaper area. If both antifungal and anti-inflammatory activity is desired, separate administration of the agents is required. Oral antifungal medications are not routinely recommended, and few data support their use. However, if an infant has concomitant oral thrush, oral nystatin suspension should also be initiated.

For cases that do not respond to conservative measures, topical corticosteroids can be applied to reduce the inflammation and pain. The corticosteroid should be discontinued immediately upon resolution of erythema. Only low-potency corticosteroids such as hydrocortisone 1%, hydrocortisone 2.5%, or desonide 0.05% should be used, with application one or two times/day for a maximum of 14 days. Mid- and high-potency steroids should not be applied underneath a diaper because this is an occlusive environment; as such, it will enhance the systemic absorption of corticosteroids and increase the risk of systemic adverse effects. In addition, the

Table 2. Topical Antifungal Agents (Reference 9)

Antifungal	Dosing Frequency	Indications
Butenafine 1% cream	Once daily	Tinea pedis
		Tinea cruris
		Tinea corporis
Clotrimazole 1% cream	Twice daily	Diaper dermatitis
		Tinea pedis
		Tinea corporis
Ketoconazole 2% foam, cream, gel	Once or twice daily	Adolescent seborrheic dermatitis
Miconazole 2% cream, powder	Twice daily	Diaper dermatitis
		Tinea pedis
		Tinea corporis
Nystatin cream or ointment	Twice daily	Diaper dermatitis
Terbinafine 1% cream, spray	Once or twice daily	Tinea pedis
		Tinea cruris
		Tinea corporis

occlusive environment of the diaper region results in an increased degree of skin atrophy. If combination therapy with both a topical corticosteroid and barrier protectant is used, the topical corticosteroid should be applied first.

If a secondary bacterial infection is suspected or no improvement in the rash is noted, the addition of topical mupirocin should be considered. Mupirocin provides gram-positive antibacterial activity, as well as some antifungal activity. For treatment of diaper dermatitis, mupirocin should be applied three times/day for 7 days.

For severe irritant dermatitis and excoriation secondary to diarrhea, applications of liquid antacids, sucralfate, or a compounded cholestyramine paste have been used (References 10, 11). Liquid antacids will act to neutralize the pH of the acidic stools. Such antacids should be applied four times/day and allowed to dry on the skin before applying a topical barrier product. Use of topical sucralfate has been reported in the adult literature, with a compounded 4% topical sucralfate preparation applied four times/day. The topical sucralfate acts as a physical barrier to protect the damaged skin. Cholestyramine paste can be compounded by mixing the powder with an ointment base to a concentration of 5% to 20%. Cholestyramine is thought to be beneficial because of its mechanism of action of binding bile acid salts (Reference 6).

Seborrheic Dermatitis

Seborrheic dermatitis is an inflammatory skin condition that can affect areas of the skin with increased sebaceous gland activity (e.g., nasolabial folds, eyebrows, scalp, ears). It can occur at any age but often has a bimodal presentation in the pediatric population. In infants, specifically within the first 3 months of life, it typically presents as cradle cap, whereas in adolescents, it presents as scalp scaling (i.e., dandruff) or erythema and scaling on the scalp, face, and trunk. The overall prevalence of seborrheic dermatitis in children is estimated to be 10% in boys and 9.5% in girls, with the highest prevalence occurring in the first 3 months of life (Reference 12). Around 42% of infants have cradle cap (Reference 12).

The exact etiology of seborrheic dermatitis is unknown; however, it has been associated with fungal infections (i.e., *Malassezia furfur,* previously *Pityrosporum ovale*), increased hormone levels, nutritional deficiencies, and neurogenic factors (Reference 13). Support for the potential link with hormone activity is that it presents in early infancy when transplacental hormones are elevated, resolves spontaneously, and then returns around puberty when another hormonal flux occurs. No firm linkage has been established with the other proposed etiologies.

Infantile seborrheic dermatitis (i.e., cradle cap) presents as thick greasy scales that are white, off-white, or yellow on the vertex of the scalp. This condition is not pruritic and does not cause discomfort to the infant, although it can be bothersome to the parent or caregiver. In addition, some infants may present with mild scaling of the face, ears, and forehead and on the flexural folds (e.g., antecubital region, popliteal region). The presence of exfoliative and widespread dermatitis may be associated with immunodeficiencies (Reference 1). The prognosis of infantile seborrheic dermatitis is generally benign and resolves by age 1 year, although there is some association with development of seborrheic dermatitis as an adult (Reference 14).

Adolescent seborrheic dermatitis presents as mild, greasy scaling of the scalp (i.e., dandruff). In addition, an oily complexion with scaling and erythema can be present in the nasolabial folds, eyebrows, postauricular skin, glabella (i.e., T-zone), and trunk. Unlike infantile seborrheic dermatitis, adolescent seborrheic dermatitis may be pruritic.

Management of cradle cap should begin with nonpharmacologic therapy, which includes non-medicated, mild shampoo and loosening of scales with a soft brush. If ineffective, emollients such as petrolatum, mineral oil, or olive oil can be applied to the scalp to loosen the scales. The emollient should be applied for a minimum of 20 minutes, but it can be left on overnight. After removal of the emollient, the scales can be gently removed by scratching the scales with a soft brush or fingertips. For more severe cases, antidandruff shampoos containing selenium sulfide or pyrithione zinc can be applied to the infant's scalp. Selenium sulfide shampoo can be safely applied twice weekly for 2 weeks and then once weekly. Parents/caregivers should be informed that it may stain the scalp reddish brown. In addition, ketoconazole shampoo has been shown to be safe and effective in infants for the treatment of infantile seborrheic dermatitis when used twice weekly for 1 month (Reference 15). No detectable levels of ketoconazole or changes in liver function tests were noted in the patients studied. Topical corticosteroids have some benefit in decreasing the inflammation associated with seborrheic dermatitis. However, these agents should not be used as a first-line option for management of cradle cap because it is considered a self-limited condition, and there is a potential for enhanced systemic absorption and skin atrophy when applied to the thin skin of the head and face. If used, low- to mild-potency agents should be recommended, and application should be limited to a small area for a short duration.

As a preventive measure, adolescents with seborrheic dermatitis should be instructed to cleanse the affected areas regularly to remove excess oil from the skin. In addition, emollients can be applied for relief

of dry skin. Antifungal (i.e., ketoconazole) or antidandruff (i.e., selenium sulfide, pyrithione zinc) shampoos are first-line pharmacologic therapy for the management of dandruff. Ketoconazole 1% shampoo should be applied twice weekly, with a minimum of 3 days between shampoos, for 8 weeks. The shampoo should be applied to wet hair and massaged over the entire scalp for 1 minute; then, it should be rinsed out and reapplied for another 3 minutes before rinsing again. Ketoconazole 2% shampoo is intended for body-wide application and should be applied to the damp skin of the affected area and left in place for 5 minutes before rinsing. A 2% ketoconazole gel has also received U.S. Food and Drug Administration (FDA) approval for treatment of seborrheic dermatitis in children 12 years and older; it is applied once daily for 2 weeks. Antifungal creams (e.g., clotrimazole, miconazole, ketoconazole) are first-line pharmacologic therapy for application to the face and can be applied once or twice daily. A short course of a topical corticosteroid may be used to relieve erythema and pruritus. Topical calcineurin inhibitors (i.e., tacrolimus and pimecrolimus) have been evaluated in the adult population as a steroid-sparing therapy for resistant seborrheic dermatitis, showing some benefit; however, further studies to evaluate efficacy are needed in the adolescent population (Reference 16). Of note, it takes up to 1 week of daily use of topical calcineurin inhibitors before efficacy is noticeable.

Atopic Dermatitis

Atopic dermatitis, also known as atopic eczema, is the most common dermatologic condition in the pediatric population, affecting up to 20% of children (Reference 17). Most children are symptomatic before they are 5 years old. The etiology of atopic dermatitis is multifactorial, with genetics, environment, and immunologic factors playing a role. Children with a diagnosis of atopic dermatitis often have a family history of atopy. Environmental factors that have been associated with atopic dermatitis include allergen exposure (e.g., pollen, mites, pets, cow's milk), irritants (e.g., soap, wool), microbial colonization, and hard water (Reference 18). Atopic individuals are thought to have early IgE (immunoglobulin E) production and impaired immune response. Patients with atopic dermatitis have inherent abnormalities in the barrier function of their skin. This impaired barrier function allows greater penetration of allergens through the skin and increased irritation. In addition, they have decreased ability to retain moisture in the stratum corneum secondary to decreased amounts of intracellular lipids and ceramides. Overall, patients with atopic dermatitis have a decreased threshold to pruritus that is typically worse in the nighttime hours. The mechanism of pruritus is not completely understood, but it is thought that histamine does not play a major role.

The clinical presentation of atopic dermatitis may differ given the age of the patient and the stage of the disease (Reference 18). In the first 2 years of life, it is characterized by pruritic, eczematous lesions that typically occur on the face, scalp, and flexor regions (i.e., antecubital space, popliteal region). The lesions become more lichenified in the childhood phase, from age 2 years to puberty, and they may involve the hands, feet, wrists, ankles, and flexor regions. The adult phase begins at puberty and affects similar regions of the previous phase, but the lesions are characterized by dry, scaling erythematous papules and plaques, and the lichenified areas are larger.

The prognosis for atopic dermatitis depends on the severity of the disease and the age of onset. This disease often involves chronic relapses, with the waxing and waning of inflammatory, pruritic lesions. Children with atopic dermatitis are at risk of the atopy triad of atopic dermatitis, allergic rhinitis, and asthma. One-half of children with atopic dermatitis in the first 2 years of life will have asthma in the following years (Reference 19). Atopic dermatitis can have a significant impact on both the child's and caregiver's quality of life. Itching at nighttime can affect sleep patterns, which in turn will result in daytime sleepiness and irritability. In addition, because of the visibility of the condition, children may feel the stigma of being different.

There is no cure for atopic dermatitis; treatment is aimed at amelioration of symptoms. The key to treatment of atopic dermatitis is prevention of an exacerbation. The mainstay of prevention is the use of emollients, which serve to increase hydration of the skin and provide a barrier. Emollients are most effective when applied continuously, whether or not inflammatory lesions are present. The maximal duration of benefit for emollients is about 6 hours; therefore, they should be applied often throughout the day (Reference 20). Ointments and creams should be recommended because they have greater occlusive properties versus lotions. Use of products that contain lanolin and fragrances should be discouraged because of the risk of contact sensitization, which may exacerbate the dermatitis. Other preventive strategies include avoidance of irritating factors or at least minimization of exposure to those agents. Exposure to water during bath time should be limited (i.e., 5 minutes or less), and tepid water should be used. In addition, mild fragrance-free soaps should be used. After bathing, the skin should be gently patted dry, and an emollient should be applied immediately to trap in the

remaining moisture. Furthermore, because scratching perpetuates dry, broken skin and can potentially introduce bacteria, fingernails should be cut short to prevent damage from scratching. In addition, cotton gloves can be worn to bed to prevent unintentional scratching while sleeping.

The treatment of acute flare-ups can be managed with topical corticosteroids as first-line therapy (Reference 20). A cross-sectional study of outpatient visits between 1997 and 2004 for pediatric atopic dermatitis noted that topical corticosteroids were underused, with topical corticosteroids prescribed in only 25% of visits from 2001 to 2004 (Reference 21). It is speculated that underuse of these agents is likely the result of concern for the adverse effects associated with topical corticosteroid use (e.g., skin atrophy, striae, systemic effects). The American Academy of Dermatology suggests that, if used appropriately, these agents are not associated with significant adverse effects. During the acute phase of the exacerbation, topical corticosteroids should be applied a maximum of twice daily because there is no further benefit with more frequent application—only an increased risk of adverse effects. Once the exacerbation is controlled (i.e., resolution of pruritus), therapy can be stepped down to a less potent preparation or discontinued. For acute symptoms, therapy with topical corticosteroids should be limited to 3–7 days (Reference 16). Chronic therapy should be limited to 2–3 weeks of continuous use. If chronic corticosteroid therapy is required beyond this period, then it is recommended to apply the topical corticosteroid on an intermittent basis at the lowest frequency of use that will control the symptoms. One example of an intermittent schedule is application of the topical corticosteroid twice weekly (References 18, 20). Topical corticosteroids, summarized in Table 3, are grouped according to potency, with group I being the most potent and group VII being the least potent. The vehicle in which the drug is contained can result in increased potency of the agent. Ointments compared with creams of the same corticosteroid have increased potency because of their occlusive nature and hydration of the skin. Increasing the solubility of the corticosteroid by adding propylene glycol can also increase the potency by increasing the amount of drug that is absorbed. These agents are often referred to as augmented. In children younger than 12 years, only low-mid to low-potency (i.e., groups V–VII) topical corticosteroids should be used. When selecting the appropriate potency, an agent with the lowest potency that will be effective for the condition should be a consideration because overdosing can increase the potential for adverse effects, and underdosing can delay benefit or result in a rebound exacerbation.

Wet wrap therapy may be used in patients with acute, oozing, and erosive lesions who are intolerant of standard topical therapy. This therapy consists of applying a layer of ointment or cream directly on the skin. The ointment or cream can be an emollient only, or it can contain a topical corticosteroid that is diluted. The area is then covered with a double layer of cotton bandages, with the first layer being moist. Application of a diluted topical steroid has resulted in greater efficacy than emollient alone (Reference 24). Recommendations for application time range from 3 to 24 hours. If the therapy includes application of diluted steroid cream, then therapy should be used once daily for up to 7 days.

Topical calcineurin inhibitors (i.e., tacrolimus, pimecrolimus) are considered second-line agents for short-term, intermittent treatment of moderate to severe atopic dermatitis in children older than 2 years. These agents target the inflammatory pathogenesis of atopic dermatitis by preventing the release of inflammatory cytokines and mediators. However, unlike corticosteroids, topical calcineurin inhibitors are not associated with skin atrophy, which allows their use on the face, eyelids, and intertriginous areas. As a result, these agents may be an appropriate alternative in children with facial atopic dermatitis. Topical calcineurin inhibitors should be applied twice daily to the affected area. Of note, only tacrolimus 0.03% has a labeled indication for children 2–15 years old, and the 0.1% ointment should not be used in this population. Long-term use of these agents is not currently recommended because there are limited studies evaluating use for prolonged periods. To date, the longest duration studied has been 2 years for pimecrolimus (Reference 25) and 4 years for tacrolimus (Reference 26). The most commonly reported adverse effect of these agents is a burning sensation at the application site in the first week of use. Use of these agents has been associated with an increased risk of infection and photocarcinogenicity. In addition, although rare in occurrence, malignancy and lymphoma are listed in a black box warning included in the agents' FDA-approved labeling. This black box warning is primarily the result of a lack of sufficient long-term safety data; no direct evidence of a causal link with cancer exists (References 16–18). Because of the concern for development of cutaneous malignancy, patients on topical calcineurin inhibitors should be encouraged to apply sunscreen regularly (SPF of 15 or greater) if exposed to ultraviolet radiation.

Systemic antimicrobials should not routinely be used for prophylaxis of infection. These agents should be reserved for diagnosed secondary infections. Likewise, use of systemic corticosteroids as long-term maintenance therapy should be avoided because the

Table 3. Potency Ratings of Selected Topical Corticosteroids (References 9, 22, 23)

Potency (Group)	Selected Representative Corticosteroids	Brand (dosage form)
Super (I)	Augmented betamethasone dipropionate	Diprolene 0.05% (ointment)
	Clobetasol propionate	Clobex 0.05% (lotion, shampoo, spray)
		Olux 0.05% (foam)
		Temovate E 0.05% (cream)
		Cormax 0.05% (ointment, solution)
		Temovate 0.05% (gel, ointment, solution)
	Fluocinonide, optimized vehicle	Vanos 0.1% (cream)
	Halobetasol propionate	Ultravate 0.05% (cream, ointment)
High (II)	Augmented betamethasone dipropionate	Diprolene AF 0.05% (cream), Diprolene 0.05% (lotion)
	Betamethasone dipropionate	Diprosone 0.05% (ointment)[a]
	Betamethasone valerate	Beta-Val 0.1% (ointment)[a]
	Fluocinonide	Lidex 0.05% (ointment, gel, cream)[a]
	Mometasone furoate	Elocon 0.1% (ointment)
Upper Mid (III)	Betamethasone dipropionate	Diprosone (0.05% cream)[a]
	Triamcinolone acetonide	Kenalog 5% (ointment)
	Fluticasone propionate	Cutivate 0.005% (ointment)
Mid (IV)	Betamethasone valerate	Luxiq 0.12% (foam)
	Hydrocortisone valerate	Westcort 0.2% (ointment)
	Mometasone furoate	Elocon 0.1% (cream, lotion)
	Triamcinolone acetonide	Kenalog 0.025%, 0.1% (ointment)
Low Mid (V)	Betamethasone valerate	Beta-Val 0.1% (cream, lotion)[a]
	Fluticasone propionate	Cutivate 0.05% (cream)
	Hydrocortisone valerate	Westcort 0.2% (cream)
	Triamcinolone acetonide	Triderm 0.1% (cream) [cream 0.025%]
Mild (VI)	Desonide	Verdeso 0.05% (foam)
		DesOwen 0.05% (cream, ointment, lotion)
		Desonate 0.05% (gel)
	Fluocinolone acetonide	Derma-Smoothe FS 0.01% (oil, shampoo) [cream 0.01%, 0.025%]
	Hydrocortisone butyrate	Locoid 0.1% (cream, solution)
Low (VII)	Hydrocortisone	Cortaid Sensitive Skin 0.5% (cream)
		Cortizone-10 Maximum Strength 1% (cream, lotion, ointment) [2.5% cream, ointment, lotion]

[a]Brand name not available or discontinued in the United States.

risks of therapy exceed the benefits. A short-term course can be used for an acute flare-up in patients with persistent, refractory disease. Oral antihistamines have a limited role in the treatment of atopic dermatitis because the pruritus is not necessarily histamine-related. A sedating antihistamine (e.g., hydroxyzine, diphenhydramine) can be recommended for use at bedtime to assist with sleep. There is no firm evidence of the efficacy of second-generation, nonsedating antihistamines (e.g., loratadine, cetirizine) in the management of atopic dermatitis (References 18, 27). Immunomodulating agents such as cyclosporine, azathioprine, and mycophenolate mofetil have been evaluated in severe cases of atopic dermatitis that are refractory to traditional therapy. Therapies that have not been proven efficacious for atopic dermatitis include delayed introduction of solid foods in infants, dietary restrictions, homeopathy, prolonged breastfeeding, and Chinese herbal therapy (Reference 28).

Pediatric Acne

Acne vulgaris is a common dermatologic condition that affects up to 87% of teenagers during their adolescence (Reference 29). Although typically thought of as an adolescent condition, acne can affect children of any age (Reference 30). Acne can have a significant impact on the quality of life of affected individuals.

The pathogenesis of acne is thought to be caused by four primary factors: sebum production, *Propionibacterium acnes* (*P. acnes*) colonization, alteration in the keratinization process, and release of inflammatory mediators into the skin (Reference 31). These four factors are interrelated and interact in a complex manner to promote the characteristic and inflammatory lesions of acne (i.e., comedone, papules, pustules, or nodules). The typical sequence of events begins with the obstruction of the hair follicle and accompanying sebaceous gland (i.e., pilosebaceous unit) by the accumulation of keratinocytes after they have been shed. This results in the formation of a microcomedo, a microscopic precursor of an acne lesion. Further obstruction leads to the formation of non-inflammatory comedones that can be open (i.e., blackheads) or closed (i.e., whiteheads). Over time, *P. acnes* will begin to proliferate within the blocked follicle and break down the sebum to free fatty acids and peptides. The immune system will then mount an inflammatory response to *P. acnes*, releasing proinflammatory mediators, thus resulting in the inflammatory lesions of acne (i.e., papules, pustules, and nodules).

The assessment of acne involves the rating of disease severity, which in turn drives the treatment pathway. Proposed strategies rate the severity of acne on the basis of lesion count or on the basis of a grading system of the total clinical presentation by accounting for lesion type, location of lesion, and involvement. To date, there are more than 25 acne-grading systems (Reference 32); however, there is no consensus on a single classification or grading system for acne.

Neonatal acne (i.e., acne neonatorum) presents within the first 4 weeks of life and affects up to 20% of neonates (Reference 24). Neonates usually present with open or closed comedones on the forehead, nose, and cheeks. In addition, papules and pustules are occasionally present. Neonatal cephalic pustulosis, which may be described or referred to as acne, presents as erythematous papulopustules but lacks the presence of comedones. The exact etiology of acne lesions in neonates is somewhat controversial, but it is believed that acne neonatorum with comedones is caused by increased androgens and that neonatal cephalic pustulosis is associated with the overgrowth of *M. furfur* (Reference 1).

Infantile acne presents between 3 and 16 months of age and is much less common than neonatal acne (Reference 24). Compared with neonatal acne, infantile acne has lesions that are more inflamed and that appear predominantly on the cheeks. In addition to comedones, papules, and pustules, infantile acne is associated with the development of cystic lesions, which have a potential to cause scarring.

The American Academy of Dermatology has established treatment guidelines and recommendations (References 25, 33). Figure 1 summarizes the treatment approach to acne, and Table 4 summarizes the medications used for acne. Topical retinoids (e.g., tretinoin, adapalene, tazarotene) are considered the first-line treatment for acute management of mild to moderate cases of acne, whether non-inflammatory or inflammatory. These agents reduce the formation of microcomedones and comedones, possess anti-inflammatory activity, and promote normal desquamation of the skin. For individuals with papular/pustular eruptions of mild to moderate severity, a topical antimicrobial agent (e.g., erythromycin, clindamycin) added to a topical retinoid is recommended for acute treatment. The combination of a topical retinoid with an antibacterial agent will address three of the four major pathogenic factors of acne. These antimicrobial agents possess activity against *P. acnes* and decrease the colonization of the skin. However, there is some concern for the development of antimicrobial resistance with the use of antibiotic therapy, and it is strongly discouraged to use antibiotics as monotherapy. Adding topical benzoyl peroxide decreases the likelihood of the emergence of resistant strains of *P. acnes*. In addition, benzoyl peroxide provides antibacterial activity. Benzoyl peroxide is available in strengths ranging from 2.5% to 10%. Because this therapy can be irritating and drying to the skin, it is recommended to initiate therapy with a lower concentration. Stronger concentrations tend to be more irritating and may not necessarily be more efficacious.

For individuals with moderate to moderately severe acne, an oral antibiotic (e.g., doxycycline, minocycline, tetracycline, erythromycin) is recommended in addition to a topical retinoid. Minocycline is considered the most efficacious oral antibiotic in decreasing *P. acnes* colonization (Reference 33). However, the tetracycline antibiotics should not be used in children younger than 8 years because of the potential for binding to calcium and being incorporated in the matrix of the tooth and bone, resulting in tooth discoloration, enamel hypoplasia, and decreased bone development. For children younger than 8 years, the oral antibiotic of choice is erythromycin. If oral antibiotics are employed, their use should be limited in duration to 3–4 months, and the need for continuation should be assessed every

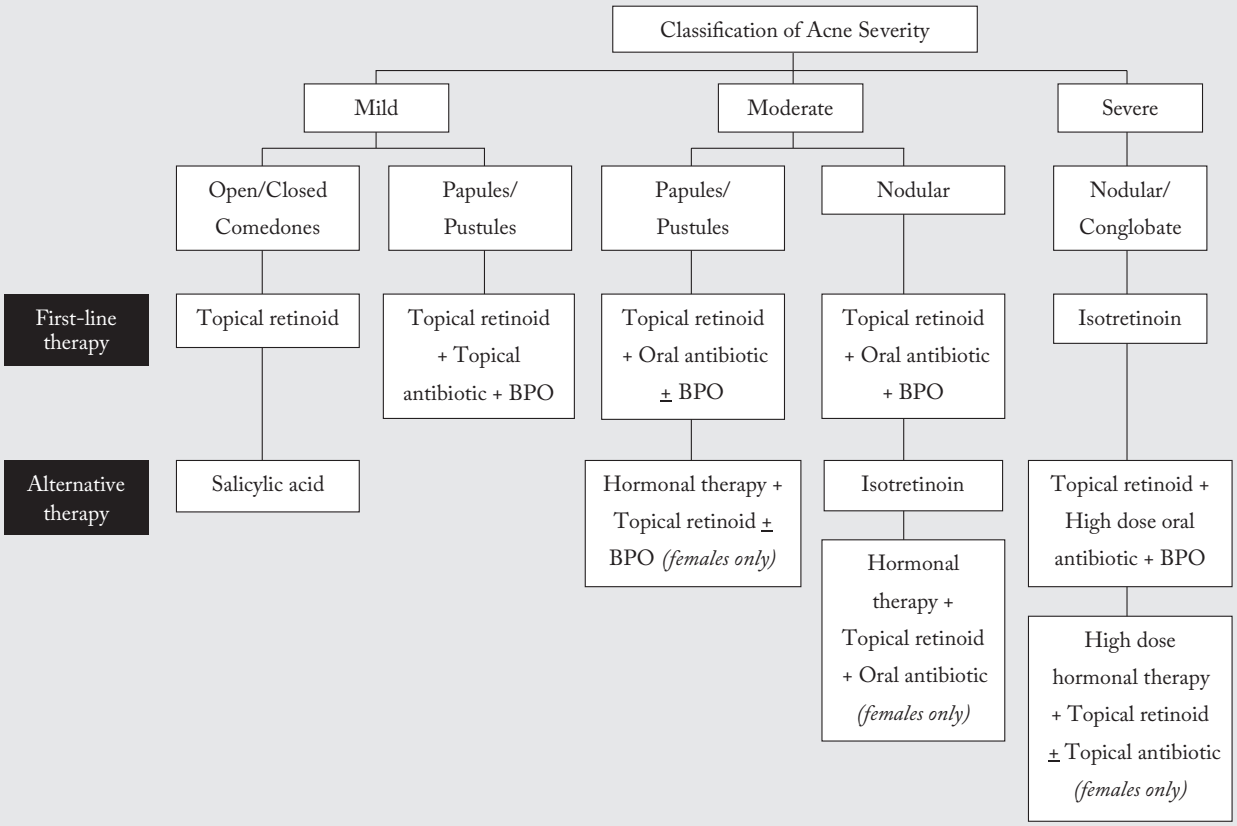


Figure 1. Recommended treatment of acne based on severity.

BPO = Benzoyl peroxide.

6–12 weeks (Reference 31). Many experts recommend against the concomitant use of oral and topical antibiotic therapy because of the increased risk of resistance and the minimal increase in therapeutic benefit (Reference 31).

There are commercially available fixed-dose products that contain a combination of therapeutic agents. These products are proposed to be more convenient for patient use by decreasing the amount of time involved in product application and will in turn promote greater adherence to therapy. A common adverse effect with combination therapy is increased skin irritation, including burning and peeling. Some data suggest that, among the retinoids, combination therapy with adapalene is best tolerated (Reference 31). In patients who are intolerant of topical retinoid therapy, topical salicylic acid can be used, although it is not considered as effective. Salicylic acid is a common ingredient in over-the-counter acne products and is available in a variety of dosage forms (e.g., creams, washes, lotions) ranging from concentrations of 0.5% to 2.0%. Other topical therapies that have limited benefit in the management of acne include azelaic acid, sulfur, resorcinol, aluminum chloride, and topical zinc.

Severe recalcitrant nodular acne requires treatment with isotretinoin. Isotretinoin decreases comedo formation by decreasing sebum production and possesses some anti-inflammatory activity. The FDA-labeled dose is 0.5–2 mg/kg/day in two divided doses for a maximum of 20 weeks. This duration can be exceeded if lower doses are used, with a maximal total cumulative dose of 120–150 mg/kg (Reference 33). Isotretinoin has several adverse effects that require monitoring throughout therapy. These include hypertriglyceridemia, hypercholesterolemia, and elevation of hepatic enzymes. Although rare, neutropenia can occur, which should be monitored periodically while receiving therapy. A causal link exists between the use of isotretinoin and the development of ulcerative colitis. The risk increases with the use of higher doses and longer durations. Overall, the absolute risk of patients who are exposed to isotretinoin is very low; however, patients should be made aware of this association. In addition, this agent has been associated with depression, aggressive behavior, and suicidal ideation. Although no direct relationship has been established in clinical studies, patients and caregivers should be informed to monitor for changes in behavior or mood.

Table 4. Acne Products (Reference 9)

Class/Selected Agents	Brand Name(s)	Dosing	Comments
Topical Agents			
Retinoids			
Adapalene 0.1%	Differin	Apply once daily in the evening.	Increased risk of photosensitivity reactions. Recommend application of sunscreen (SPF ≥ 15)
Tazarotene 0.05%, 0.1%	Tazorac	Apply 2 mg/cm^2 once daily in the evening.	
Tretinoin 0.025%, 0.05%, 0.1%	Retin-A, Avita	Apply once daily in the evening; start with 0.025% cream or 0.01% gel and increase concentration as tolerated.	
Antibiotics			
Clindamycin 1%	Cleocin T, ClindaMax	Apply a thin film twice daily.	Should not be used as monotherapy
Erythromycin 2%	Akne-mycin	Apply twice daily.	
Benzoyl peroxide 2.5%, 4%, 5%, 8%, 10%	Neutrogena Clear Pore, Benzac AC, OXY	Apply once daily; can gradually increase to two or three times/day, if needed	If excessive dryness or peeling occurs, reduce dose frequency or concentration. Recommend application of sunscreen (SPF ≥ 15)
Keratolytic Agent			
Salicylic acid 0.5% to 2%	Clean and Clear Advantage Acne Cleanser, Neutrogena Oil-Free Acne Stress Control, OXY face wash	Apply once or twice daily.	Available in a variety of dosage forms. Recommended in patients who cannot tolerate benzoyl peroxide. Do not use in children < 2 years.
Combination Products			
Erythromycin/ Benzoyl peroxide	Benzamycin	Apply twice daily.	
Clindamycin/ Benzoyl peroxide	Acanya, BenzaClin	Apply pea-sized amount once daily (Acanya). Apply twice daily (BenzaClin)	
Clindamycin/ Tretinoin	Veltin, Ziana	Apply once daily.	Increased risk of photosensitivity reactions. Recommend application of sunscreen (SPF ≥ 15)
Adapalene/ Benzoyl peroxide	Epiduo	Apply once daily.	Increased risk of photosensitivity reactions. Recommend application of sunscreen (SPF ≥ 15)

(continued)

Table 4. Acne Products (Reference 9) *(continued)*

Class/Selected Agents	Brand Name(s)	Dosing	Comments
Systemic Agents			
Antibiotics			
Tetracycline	—	Adolescents: 500 mg twice daily	Should not be used in children < 8 years because of effects on teeth and bone; increased risk of photosensitivity reactions. Recommend application of sunscreen (SPF ≥ 15). Avoid taking with calcium- or iron-containing products.
Doxycycline	Vibramycin	Adolescents: 50–100 mg/dose once or twice daily	
Minocycline	Minocin, Dynacin, Solodyn & Ximino (extended release)	Adolescents: 50–100 mg/dose once or twice daily Extended-release product (Solodyn): Children > 12 years: About 1 mg/kg daily: 45–49 kg: 45 mg once daily 50–59 kg: 55 mg once daily 60–71 kg: 65 mg once daily 72–84 kg: 80 mg once daily 85–96 kg: 90 mg once daily 97–110 kg: 105 mg once daily 111–125 kg: 115 mg once daily 126–136 kg: 135 mg once daily	
Erythromycin	E.E.S., EryPed	250–500 mg twice daily	Several drug interactions, inhibitor of CYP3A4
Hormonal Therapy			
Oral contraceptives	Ortho Tri-Cyclen, Estrostep Fe, Yaz	Take 1 tablet daily.	May take up to 4 months for efficacy
Spironolactone	Aldactone	50–100 mg twice daily	Potassium-sparing, can cause hyperkalemia
Retinoic Acid Derivative			
Isotretinoin	Claravis, Amnesteem, Sotret, Absorica	0.25–0.5 mg/kg/dose twice daily; maximal dose of 1 mg/kg twice daily	Do not use in pregnancy, iPLEDGE registration. Recommend application of sunscreen (SPF ≥ 15)

CYP = cytochrome P450; SPF = skin protection factor.

Isotretinoin is rated pregnancy category X and has a black box warning against use in pregnancy. Because of this teratogenic risk, all patients (male or female), prescribers, manufacturers, wholesalers, and dispensing pharmacies must be registered in the iPLEDGE risk management program. Females of childbearing age should have two negative pregnancy tests, a minimum of 19 days apart, before therapy initiation. According to the iPLEDGE program, two forms of contraception should be used 1 month before, during, and 1 month after isotretinoin therapy. Prescriptions can only be written for a 30-day supply, and a pregnancy test should be completed monthly.

Use of hormone therapy with estrogen-containing contraceptive agents can be considered in female patients with mild to moderate acne due to their antiandrogenic effects. Oral contraceptives with FDA approval for the management of acne include ethinyl estradiol/norgestimate, ethinyl estradiol/norethindrone, and ethinyl estradiol/drospirenone, although it is expert opinion that any estrogen-containing contraceptive would be equally effective (Reference 33). Patients should be educated that improvement in acne lesions may take up to 4 months with these agents (Reference 34). Another agent that has been evaluated in the treatment of acne because of its antiandrogen activity is spironolactone at

doses of 50–200 mg/day. Patients on this therapy should be monitored for hyperkalemia, specifically when higher doses are used.

After initial treatment of active lesions, maintenance therapy should be initiated to prevent a rebound exacerbation of acne. For all acne types, a topical retinoid should be recommended for maintenance therapy, with the addition of benzoyl peroxide if more antibacterial activity is needed. Adapalene 0.3% and adapalene 0.1%/benzoyl peroxide 2.5% have been studied most extensively for long-term use up to 1 year (Reference 31). Experts recommend applying the maintenance product to the entire affected area, not just to the area of concern. This is because microcomedones are not detectable by the naked eye, and topical retinoid therapy will decrease the formation of microcomedones. Use of antibiotics for maintenance therapy should be discouraged. Nonpharmacologic recommendations for the patient should include washing of the skin with a gentle cleanser twice daily and application of a noncomedogenic moisturizer. Individuals should avoid too frequent or too harsh washing because this may worsen the acne. Consumption of certain foods has anecdotally been associated with worsening acne; however, no studies support this belief. Therefore, according to the guidelines, dietary restriction is of no benefit in the management of acne (Reference 33).

Typically, treatment of neonatal acne is unnecessary, and parents/caregivers should be reassured that this is a transient condition that should resolve around age 3 months in most cases (Reference 30). Parents can be instructed to cleanse the face with a gentle soap and water. In more severe cases, neonates can be treated with 2.5% benzoyl peroxide lotion. If colonization with *Malassezia* is suspected, application of 2% ketoconazole cream twice daily for 1 week has been shown efficacious (Reference 1). The management of infantile acne is similar to that of older children and adolescents. First-line therapy continues to be a topical retinoid with or without benzoyl peroxide plus or minus a topical antibiotic. A small open-label study has shown that adapalene gel is both safe and efficacious for mild to moderate acne in children younger than 24 months (Reference 35). If an oral antibiotic is necessary, erythromycin is the medication of choice in this population because of the relative contraindication of tetracyclines. For severe, recalcitrant cases of infantile acne associated with scarring, use of oral isotretinoin has been reported in infants as young as 5 months, with doses ranging from 0.2 to 2 mg/kg/day in two divided doses (Reference 30). Administering this medication in the infant population may present some technical difficulties because it is commercially available only in tablet and capsule forms. Most cases of infantile acne will resolve by age 4–5 years.

Dermatophyte Fungal Infections

Ringworm fungi are dermatophytes that include species of *Microsporum, Trichophyton,* and *Epidermophyton.* These fungi are typically able to survive only in the stratum corneum, hair, and nails. The infections described in the following sections are considered *tinea*, or fungal infections that are further classified by the body region infected.

Tinea Corporis

Tinea corporis, or ringworm that presents on the body, is typically caused by *Trichophyton* spp. It presents as a round, but irregular, scaly spot that develops a raised border and central clearing. The border may be red with raised papules. Lesions may be small or may appear to spread.

Topical antifungals, summarized in Table 2, are sufficient to treat most cases of tinea corporis. The antifungal should be applied to the lesion and the 2 cm surrounding it. Therapy continues for 14 days, or for 1 week after clinical resolution, to ensure fungal eradication. Newer therapies, terbinafine and butenafine, are fungicidal and are considered more effective than miconazole and clotrimazole (Reference 36). Combination products containing corticosteroids and antifungals are not recommended. Cases that are more extensive may be treated with systemic fluconazole, itraconazole, or terbinafine.

Tinea Pedis

Tinea pedis, or athlete's foot, is caused by *Trichophyton* or *Epidermophyton* spp. It is less common in prepubertal children. Tinea pedis presents as a white area between the toes, or dry scaling accompanied by itching. Exposure to a moist environment predisposes the feet to fungal infections.

Terbinafine and butenafine produce higher cure rates and more rapid resolution than miconazole or clotrimazole (Reference 37). Treatment with terbinafine and butenafine typically requires 1–2 weeks. Miconazole and clotrimazole will require 2–4 weeks of treatment. As with tinea corporis, treatment should continue for 1 week beyond clinical resolution. Antifungal powders can be applied to the feet to decrease moisture. Nonpharmacologic therapy includes exposing the feet to air as often as possible.

Tinea Cruris

Tinea cruris, also known as jock itch, is an infection of the groin caused by *Trichophyton* or *Epidermophyton* spp. It is most common in postpubertal males, but it is seen in females. The rash is typically reddish brown and symmetric with defined borders, typically sparing the scrotum. The rash is usually pruritic, and it may burn.

Treatment should consist of either terbinafine cream or spray for 1 week or butenafine cream for 2 weeks (Reference 36). Agents such as miconazole, clotrimazole, econazole, and ciclopirox are generally not

recommended for tinea cruris because their fungistatic nature requires a longer treatment and may present a problem with adherence to the regimen.

Tinea Capitis

The most common fungal infection in children is tinea capitis, or tinea of the scalp, occurring in an estimated 4% of the U.S. population, with a higher incidence in those of African American descent and in developing countries (Reference 38). In the United States, most tinea capitis cases are caused by *Trichophyton tonsurans*, with some cases caused by *Microsporum* spp. Other countries typically have a predominance of *Microsporum* spp.

Children with tinea capitis present with itching, scaling of the scalp, or circular patches of hair loss. When more inflammation is present, there are pustules as well. Those with more persistent infection and inflammation may present with kerion lesions, which are boggy, tender, and pustular (Reference 38). A diagnosis can typically be made from clinical presentation, but a fungal culture can be obtained to confirm the diagnosis and identify the infecting fungus.

Treatment of tinea capitis requires prolonged systemic therapy to penetrate the infected hair shaft. Griseofulvin is considered the drug of choice in children, but fluconazole, terbinafine, and itraconazole are effective alternatives. Each agent has similar efficacy when treating *Trichophyton* spp., but terbinafine is inferior to griseofulvin, fluconazole, and itraconazole for treating *Microsporum* spp. (Reference 39). Treatment of *Microsporum* infections requires longer therapy than does *Trichophyton*. Treatment regimens for tinea capitis are summarized in Table 5.

Griseofulvin is available in microsize suspension and tablets and in ultramicrosize tablets. Because of poor water solubility, griseofulvin should be given with a fatty meal to increase absorption. Common adverse effects include gastrointestinal upset (often leading to treatment discontinuation), headache, and rash. Dividing the daily dose may decrease the incidence of gastrointestinal complaints. More rarely, elevated liver function tests and granulocytopenia are reported. Monitoring a complete blood cell count and liver function is recommended for treatment lasting longer than 8 weeks.

Terbinafine is available as a 250-mg tablet or as 125-mg and 187.5-mg packets of granules for sprinkling on nonacidic food, such as pudding or mashed potatoes. An advantage of terbinafine is the shorter therapy duration required for *Trichophyton* spp., which may improve adherence. Common adverse effects include vomiting, nausea, loss of appetite, and itching. More rarely, elevated liver function tests and hepatic failure in those with preexisting liver disease have been reported. Liver function tests are recommended before initiating therapy and if terbinafine is continued longer than 6 weeks.

Fluconazole has a favorable safety profile in children and is available in liquid and tablet formulations, making it a reasonable alternative to griseofulvin. Common adverse effects include gastrointestinal issues, headache, and rash. Elevated hepatic enzymes are a rare complication of fluconazole therapy.

Table 5. Treatment Regimens for Tinea Capitis (References 38–40)

Antifungal	Dose	Treatment Duration (weeks)	Treatment Considerations
Griseofulvin microsize	20–25 mg/kg/day in one or two divided doses up to 1000 mg/day	6–12	Monitor liver function if duration exceeds 8 weeks.
Griseofulvin ultramicrosize	10–15 mg/kg/day in one or two divided doses up to 750 mg/day	6–12	Monitor liver function if duration exceeds 8 weeks.
Terbinafine	< 25 kg: 125 mg/day 25–35 kg: 187.5 mg/day > 35 kg: 250 mg/day	2–6	Monitor liver function before treatment and if duration exceeds 4 weeks.
Fluconazole	6 mg/kg/day OR 8 mg/kg once weekly	3–6 6–12	Limited data available
Itraconazole	Capsules: 5 mg/kg/day Oral solution: 3 mg/kg/day	2–6	Monitor liver function before treatment and if duration exceeds 4 weeks. A pulse regimen of daily dosing 1 week each month for 2–4 months has been studied in adults.

Itraconazole is available as capsules and liquid. The capsules should be given with food, and the liquid should be given on an empty stomach. Although an intermittent regimen involving daily dosing for 1 week each month for a total of two or four cycles has been studied in adults, there are no pediatric data to confirm the efficacy of this regimen. Common adverse effects include headache, rash, and gastrointestinal complaints. Elevated liver function tests were a rare complication of itraconazole therapy in tinea capitis studies.

Treatment should generally be continued until hair regrowth is evident or about 2 weeks after clinical resolution. The long therapy duration often results in nonadherence and treatment failure. Topical treatment with selenium sulfide or ketoconazole shampoo may decrease the carriage of spores, thus reducing transmission to others and reinfection. Shampoos should be used twice weekly for 2–4 weeks as an adjunct to systemic therapy.

Tinea Unguium

Tinea unguium is a type of onychomycosis affecting the fingernails or toenails, usually caused by *Trichophyton rubrum* in children (Reference 8). Although it is generally considered a cosmetic problem, it can cause a loss of self-esteem and precipitate complications in those with underlying diseases such as diabetes. It is less common in prepubertal children and has a higher incidence in children with Down syndrome (Reference 8).

The clinical presentation includes discoloration and possibly flaking or dystrophy of the nail. Children typically have a distal presentation called distal lateral subungual onychomycosis (Reference 8). Other types of onychomycosis include proximal subungual and superficial white onychomycosis. The latter affects only the nail plate, not the nail bed.

In children with superficial onychomycosis and distal involvement not exceeding one-third of the nail bed, topical therapy with ciclopirox 8% nail lacquer may be attempted. The lacquer is applied daily, with removal once a week, for 48 weeks (Reference 42). The cure rate is low, and relapse is common. In infants and young children, the nail bed is thinner, and topical therapies may be more effective (Reference 8). Topical therapy is also recommended for anyone who is not an appropriate candidate for systemic therapy.

Systemic therapy is recommended for most cases of onychomycosis. Treatment of the toenails requires a longer duration than for fingernails. The most effective therapy is terbinafine. Additional treatment options include itraconazole and fluconazole, with fluconazole as the least effective option. The fingernail will usually look normal before the fungus is eradicated, making it very important to emphasize that treatment should continue for the complete duration to avoid relapse. Table 6 summarizes treatment regimens for tinea unguium in children.

Molluscum Contagiosum

Molluscum contagiosum is a localized skin infection caused by a virus in the poxvirus family. It is usually seen in children, but it can present in adults more commonly as a sexually transmitted variant. Infection occurs after contact with an infected individual or an object harboring the virus. Swimming pools and baths are another source of transmission. Molluscum contagiosum is most common in children 2–5 years old and has a reported prevalence of 5% to 7% in elementary schools, resulting in almost 300,000 office visits each year (Reference 43).

Molluscum typically presents as one or many shiny, white or flesh-colored papules with a dimple in the center. With time, there may be crusting or fluid production as the lesion begins to destruct. Most cases will resolve spontaneously, but this may take up to 9 months because of the spread of the virus. In some cases, the

Table 6. Treatment Regimens for Tinea Unguium in Children (References 8, 42)

Antifungal	Dose	Duration
Terbinafine	< 20 kg: 62.5 mg/day 20–40 kg: 125 mg/day > 40 kg: 250 mg/day	Toenail: 12 weeks Fingernail: 6 weeks
Itraconazole capsules	Pulse with 5 mg/kg/day, 1 week/month Up to 400 mg/day	Toenail: 3 pulses Fingernail: 2 pulses
Itraconazole solution	Pulse therapy 3–5 mg/kg/day, 1 week/month	Toenail: 3 pulses Fingernail: 2 pulses
Fluconazole	3–6 mg/kg, one dose per week	Toenail: 26 weeks Fingernail: 12 weeks

lesions may persist for up to 4 years. They are generally not harmful, except that they can be spread to others. In addition, in individuals with atopic dermatitis, local irritation and inflammation often occur.

In those with normal immune function, therapy is not typically indicated. However, treatment may be helpful in the following situations: lesions associated with discomfort or itching, cosmetic reasons or social stigma, limiting spread to others, and secondary infections. Therapy may consist of physically destroying the lesions, applying topical treatments, or using systemic treatment. Physical removal with a sharp curette or liquid nitrogen is most effective, but this can be painful and can lead to scarring. Topical treatments may include cantharidin or imiquimod. Cantharidin is applied in the medical provider's office; then, it is washed off after 4–6 hours and repeated every 2–4 weeks until resolved (Reference 37). Imiquimod is applied nightly, 5–7 days/week, for at least 12 weeks. Imiquimod is slower acting, but it provides an advantage of being painless compared with physical removal. Other topical agents that have been used, but that are generally not recommended, are podofilox, retinoids, salicylic acid, and potassium hydroxide. Systemic cimetidine has been studied using 35 mg/kg/day for 4 months; however, no significant difference from placebo was observed. Currently, there is insufficient evidence to choose one therapy over another (Reference 43), but a recent survey determined that dermatologists usually use no intervention, or they use cantharidin, imiquimod, curettage, or cryotherapy (Reference 44).

Conclusions

Because of the high prevalence of dermatologic conditions in childhood, pharmacists will have opportunities to help determine age-appropriate therapy and provide patient and caregiver education. Knowledge of the unique aspects of topical medication delivery and common irritants to avoid in infants and children will help ensure the best care for this population.

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PART II

Cardiovascular/ Pulmonary

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Section Editor

CHAPTER 9

Congenital Heart Disease

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Learning Objectives

1. Understand the basic pathophysiology of common congenital heart defects.
2. Be able to select and appropriately monitor pharmacotherapy for a patient with a congenital heart defect.
3. Understand the pathophysiology, diagnosis, and pharmacotherapy for treatment of low cardiac output syndrome.

Abbreviations in This Chapter

ASD	Atrial septal defect
BT	Blalock-Taussig (shunt)
HLHS	Hypoplastic left heart syndrome
LA	Left atria
LCOS	Low cardiac output syndrome
PDA	Patent ductus arteriosus
PGE	Prostaglandin
PLE	Protein-losing enteropathy
PVR	Pulmonary vascular resistance
RA	Right atria
SVR	Systemic vascular resistance
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
VSD	Ventricular septal defect

Introduction

Congenital heart disease is the most common birth defect, occurring in about 8 of every 1000 live births (References 1, 2). The first repair of a congenital heart defect occurred in 1945 in a patient with tetralogy of Fallot (TOF). Alfred Blalock and Helen Taussig created a Blalock-Taussig (BT) shunt (an attachment of the subclavian artery to the pulmonary artery [PA]) to treat the patient, and they subsequently published their experience (Reference 3). Since then, tremendous strides have occurred in the diagnosis, repair, and management of congenital heart disease (Reference 4). However, similar strides have not been made in the application of pharmacotherapy to pediatric patients with congenital heart disease.

Recent publications have shown a lack of data supporting pharmacotherapy in pediatric cardiology patients and considerable variation in practice, with several studies showing no effect of pharmacotherapy on patient outcomes (References 5–8). In addition, many patients with congenital heart disease have several cardiac defects, involvement of other organ systems (i.e., asplenia and intestinal malrotation in patients with heterotaxy syndrome), or genetic mutations (i.e., Down syndrome with complete atrioventricular canal) that can complicate pharmacotherapy (References 1, 2). Moreover, strategies for managing congenital heart disease are often subject to institutional bias. For example, institutions vary in their use of corticosteroids in the cardiopulmonary bypass circuit, recombinant factor VIIa to control postoperative bleeding, or peritoneal dialysis as a strategy for removing fluid and inflammatory mediators in postoperative patients, all of which could potentially affect pharmacotherapy (References 9–12).

Because the pharmacotherapy for congenital heart disease can be complex, a complete understanding of pathophysiology, hemodynamics, and pediatric pharmacology is necessary to appropriately use medications. This chapter aims to summarize the pathophysiology and pharmacotherapy for common congenital heart defects in pediatric patients. This discussion includes the epidemiology of congenital heart defects, clinical presentation, diagnosis, course and prognosis of the disease, and surgical or interventional procedures associated with the various defects. Each defect presented is evaluated as if a patient were presenting with an isolated lesion. Reality, however, is much more complex, and many congenital heart defects occur in combination with other comorbidities.

The pharmacotherapy for each congenital heart defect will be summarized with respect to the preoperative (or surgically unrepaired) period, the immediate postoperative period, and the long-term (or chronic) management of surgically repaired congenital heart disease.

Tables 1 and 2 summarize the surgical management, common complications, and basic pharmacotherapy for each of the lesions (Reference 13). Because a large portion of the pharmacotherapy for congenital heart disease is in the immediate postoperative period, the etiology, diagnosis, and treatment of postoperative low cardiac output syndrome (LCOS) will be addressed.

Table 1. Common Congenital Heart Defects and Surgical Repairs

Defect	Description of Lesion	Surgical (or Interventional) Repair
Patent ductus arteriosus (PDA)	Communication between pulmonary artery (PA) and aorta	Ductus ligation Coil or device insertion (interventional)
Atrial septal defect (ASD)	A communication between right and left atria by a hole in the atrial septum	Patch repair of defect[a] Device insertion (interventional)
Ventricular septal defect (VSD)	A communication between right and left ventricles by a hole in the ventricular septum	Patch repair of defect[a] Device insertion (interventional)
Tetralogy of Fallot (TOF)	PA stenosis, VSD, overriding aorta, right ventricular hypertrophy	VSD closure and repair of PA stenosis[a]
Transposition of the great arteries (TGA)	Switched locations of the PA and aorta, resulting in two separate circulations	Arterial switch operation[a]
Coarctation of the aorta (CoA)	Narrowing of the aorta. Grouped into pre- and postductal categories	End-to-end anastomosis surgery (if the coarctation does not involve carotid arteries) Patch repair surgery[a] (if coarctation involves carotid arteries)
Hypoplastic left heart syndrome (HLHS)	Absence of left ventricle and aortic narrowing (atresia)	Norwood procedure[a] (combination of PA and aorta to form a "neo-aorta," BT shunt, atrial septectomy) OR Sano modification[a] OR hybrid procedure
Bidirectional Glenn	Second stage of HLHS palliation	Takedown of BT shunt, anastomosis of SVC to PA[a]
Fontan	Third stage of HLHS palliation	Attachment of IVC to PA by an extracardiac conduit[a]

[a]Requires cardiopulmonary bypass to perform surgical procedure.
BT = Blalock-Taussig; IVC = inferior vena cava; SVC = superior vena cava.

Table 2. Significant Sequelae of Congenital Heart Disease Before and After Surgical Intervention

Defect	Preoperative	Immediate Postoperative	Long Term
Patent ductus arteriosus (PDA)	CHF, PHTN	None	None
Atrial septal defect (ASD)	CHF, PHTN	HTN	None
Ventricular septal defect (VSD)	CHF, PHTN	Systolic HTN, arrhythmias	None
Tetralogy of Fallot (TOF)	CHF, hypercyanotic episodes, chronic cyanosis, clubbing	LCOS, PHTN, HTN, VT, thrombus formation	VT, exercise intolerance
Transposition of the great arteries (TGA)	Cardiogenic shock, cyanosis	LCOS, coronary vasospasm	None (arterial switch)
Coarctation of the aorta (CoA)	Cardiogenic shock (neonates), CHF, LV enlargement	LCOS (particularly in neonates), HTN	HTN, recoarctation
Hypoplastic left heart syndrome (HLHS)	Cardiogenic shock, cyanosis	LCOS, arrhythmias, PHTN, cyanosis	Sudden death, low weight gain, poor feeding
Bidirectional Glenn	See long-term HLHS management	LCOS, arrhythmias, PHTN	CHF
Fontan	See long-term bidirectional Glenn management	LCOS, arrhythmias, PHTN, chylous effusions, thrombus formation	Arrhythmias, effusions, PLE, thrombi, plastic bronchitis

CHF = congestive heart failure; HTN = hypertension; LCOS = low cardiac output syndrome; LV = left ventricular; PHTN = pulmonary hypertension; PLE = protein-losing enteropathy; VT = ventricular tachycardia.

A brief overview of fetal versus neonatal circulation is included, but we will focus on the role each plays in neonatal congenital heart disease. Because the care of patients with congenital heart disease can be multifaceted, this chapter will only focus on the pathophysiology and pharmacotherapy related directly to congenital heart defects and will not cover areas such as postoperative pain and sedation management or infectious disease prophylaxis. In addition, the normal circulation and structure of the heart will not be presented, and the reader is encouraged to understand the anatomy and physiology of the normal heart before reading this chapter.

Low Cardiac Output Syndrome

The patient with LCOS is encountered primarily after surgical repair of congenital heart disease. Low cardiac output syndrome is often defined as the inability of the heart to deliver oxygenated blood to the end organs and tissues to satisfy demand or consumption (References 14–16). The primary etiology of LCOS is the myocardial "stunning" that occurs after cardiac surgery, together with higher circulating levels of interleukins and other inflammatory mediators. The use of cardiopulmonary bypass is often implicated in LCOS, as is aortic cross clamping during surgery (resulting in myocardial ischemia), myocardial tissue incision, and the use of cardioplegia solutions (References 14, 17). Studies have shown a decline in cardiac output, an increase in pulmonary vascular resistance (PVR), and an increase in systemic vascular resistance (SVR) occurring 6–18 hours after cardiac surgery, particularly in neonates that have undergone cardiopulmonary bypass during surgery (References 15, 16, 18).

Low cardiac output syndrome is diagnosed on the basis of a collection of symptoms. Subjectively, patients may look gray or dusky, as opposed to pink, with a sluggish capillary refill time (greater than 3 seconds). They may also have cool peripheral temperatures compared with their core body temperature. Patients with LCOS will show signs of decreased end organ and tissue perfusion, including decreased urine output and metabolic acidosis, with elevated serum lactate levels from poorly perfused tissues undergoing anaerobic metabolism (References 15, 16, 19).

The role of pharmacotherapy in the postoperative patient with congenital heart disease is to prevent or minimize LCOS. The basis of pharmacotherapy is to manipulate stroke volume given the classic equation for cardiac output (cardiac output = stroke volume × heart rate) (Figure 1). Optimizing preload, reducing afterload, and augmenting contractility are, in general, methods by which pharmacotherapy is used to improve cardiac output. These methods will be discussed throughout this chapter, and a summary of medications used in the immediate postoperative period has been provided (Table 3).

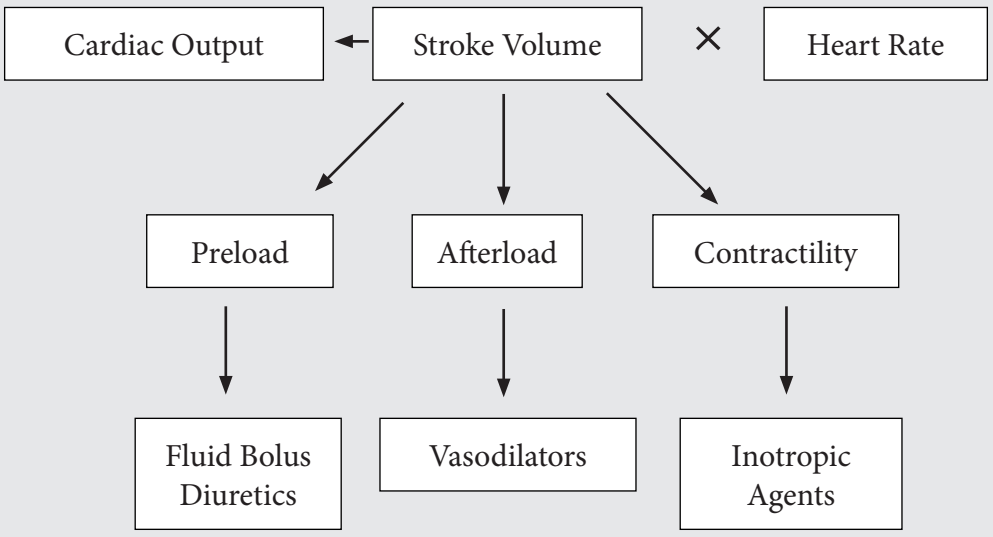


Figure 1. Pharmacologic manipulation of cardiac output.

This diagram represents the common thought process for pharmacologic manipulation of cardiac output in a postoperative surgical patient with congenital heart disease. By optimizing preload, the myocardium will respond by increasing cardiac output, as demonstrated by the Frank-Starling curve. Reduction in afterload allows less resistance on ejection of blood from the ventricle, and an increase in contractility (inotropy) improves the force on which blood is ejected. Each of these areas can be manipulated pharmacologically to improve cardiac output.

Table 3. Common Continuous-Infusion Inotropic, Vasopressor, and Vasodilator Agents

Drug	Dosing	Mechanism of Action	Effects
Dobutamine	2.5–20 mcg/kg/minute	β_1, β_2-agonist	Myocardial contractility, peripheral vasodilation
Dopamine	2–20 mcg/kg/minute	Dopaminergic (2–5 mcg/kg/minute) agonist β_1 (5–10 mcg/kg/minute) agonist α (10–20 mcg/kg/minute) agonist	Renal vasodilation (?) Myocardial contractility Peripheral vasoconstriction
Epinephrine	0.01–1 mcg/kg/minute	β_1, α_1, β_2-agonist (more β_1 and less α_1 at lower doses)	Myocardial contractility, peripheral vasoconstriction
Fenoldopam	0.2–0.8 mcg/kg/minute	Dopamine-1 receptor agonist	Peripheral vasodilation
Milrinone	0.375–0.75 mcg/kg/minute	Phosphodiesterase-3 inhibitor	Myocardial contractility, vasodilation
Nesiritide	0.01–0.03 mcg/kg/minute	B-type natriuretic peptide	Vasodilation
Nicardipine	0.5–5 mcg/kg/minute	Dihydropyridine calcium channel blocker	Vasodilation
Nitroprusside	0.5–4 mcg/kg/minute	Generation of nitric oxide	Vasodilation
Norepinephrine	0.05–1 mcg/kg/minute	α_1, β_1-agonist	Peripheral vasoconstriction, myocardial contractility
Phenylephrine	0.1–0.5 mcg/kg/minute	α_1-agonist	Peripheral vasoconstriction
Prostaglandin E1	0.01–0.4 mcg/kg/minute	Direct effect on vascular smooth muscle	Vasodilation
Vasopressin	0.0003–0.002 unit/kg/minute	V1 and V2 receptors	Vasoconstriction, water retention

Preload

Optimizing preload is essential for maintaining maximal cardiac output. If preload is too high, patients will experience venous congestion and edema, but if preload is too low, cardiac output is diminished. Monitoring of preload is based on the patient's physical examination (e.g., hepatomegaly, pulmonary edema), or it can be evaluated in patients with direct right atrial pressure monitoring (Reference 13). Appropriate preload can be titrated using crystalloid or colloid solutions administered as continuous infusions or intermittent boluses (Reference 20). Preload reduction usually occurs with diuresis. Loop diuretics are commonly used as the pharmacologic agent of choice for fluid removal in a cardiac patient (References 21–23). Furosemide may be administered as an intermittent or continuous infusion, but continuous infusions have shown benefit in maintaining diuresis while limiting exposure to medications (References 24, 25). Bumetanide and torsemide have also been used, but with less published literature (References 26, 27). Thiazide diuretics or spironolactone can also be used, particularly when patients begin to experience diuretic resistance (Reference 28). Potassium supplementation may be necessary in patients receiving high doses of diuretics (Reference 29). Hypochloremic metabolic alkalosis is an adverse event associated with high doses and long-term therapy with loop diuretics. The use of acetazolamide and/or chloride supplementation may be necessary in some patients to reverse the alkalosis (References 13, 30).

Afterload

Reduction in afterload is primarily accomplished by medications that dilate the systemic vasculature. Dobutamine, fenoldopam, milrinone, nitroprusside, nicardipine, and nesiritide are examples of continuous-infusion agents that promote systemic vascular dilation. Milrinone is the agent listed with the most supportive literature associated with pediatric postoperative cardiac surgical patients, including pharmacokinetic data (References 17, 31–35). Patients taking these agents should be monitored for potential adverse events including arrhythmias (dobutamine), thrombocytopenia (milrinone), cyanide toxicity with high doses (greater than 2 mcg/kg/minute) of nitroprusside, and hypotension (all) (References 17, 31–44). Nesiritide has preload reducing effects, in addition to vasodilatory effects, but has been noted to cause acute kidney injury (References 45–54). The vasodilatory effects of fenoldopam tend to

be less potent than those of other agents, but reports have been published of its utility in increasing urine output in patients receiving high doses of diuretics (References 55, 56). Angiotensin-converting enzyme inhibitors (ACEIs) (e.g., captopril, enalapril) have also been used as oral afterload-reducing agents (References 7, 57–62). Enalaprilat provides an intravenous form of ACEI that may be used in patients who are unable to take oral medication. In particular, hypotension and acute kidney injury have been observed when using ACEIs in patients with congenital heart disease (References 13, 62–66).

Although this section has focused on systemic cardiac output, many patients also require pharmacologic manipulation of the pulmonary vasculature to improve cardiac output to the lungs. Agents such as nitric oxide, sildenafil, epoprostenol, and iloprost have been used to augment cardiac output to the pulmonary vascular bed (References 67–79).

Inotropy

Increased contractility (inotropy) in the immediate postoperative period can be achieved with a wide variety of continuous-infusion medications. Dobutamine, dopamine, epinephrine, norepinephrine, and milrinone can be used to improve myocardial contractility. Catecholamines, such as epinephrine and norepinephrine, should be used in lower doses to improve contractility and minimize peripheral vasoconstriction and increased afterload. Dopamine may be used as an inotropic agent, but reports have associated its use with an increase in postoperative arrhythmias (References 80, 81). Dobutamine can be used as an inotropic agent with the beneficial effect of reduced afterload from peripheral vasodilation, but arrhythmias have also been noted with its use (References 36–38).

Catecholamine refractory shock can occur in patients with profound vasodilation and myocardial depression. Vasopressin is an agent that can be considered in patients with catecholamine refractory shock. Vasopressin is a potent vasoconstrictor that, when used at very low doses, has profound effects on the periphery and the coronary arteries (References 82–87). Bolus administration of hydrocortisone has also been shown to improve catecholamine responsiveness and hemodynamic parameters (Reference 88).

Pharmacotherapy should be applied in a selective manner that incorporates not only the patient's cardiac pathophysiology, but also other comorbidities and pathophysiologies that are present (Figure 2). Pharmaceutical management depends on the patient's cardiac pathophysiology, and nonpharmacologic options, such as peritoneal dialysis, new ventilator strategies, or mechanical support, are often employed (References 11, 12, 14). A comprehensive understanding of the pharmacology and physiologic effects of medications used for the prevention and treatment of LCOS is necessary to make informed decisions.

Fetal vs. Neonatal Circulation

One of the primary differences between fetal circulation and neonatal circulation, as it pertains to congenital heart disease, is the oxygenation of blood by the placenta instead of the lungs. Fetal pulmonary vasculature is typically constricted, allowing only a small amount of blood to the lungs. The lungs are bypassed in utero by three shunts: the ductus venosus (connecting the inferior vena cava to the umbilical vein), the ductus arteriosus (connecting the PA to the aorta), and the foramen ovale (a communication through the atrial septum connecting the left atria [LA] and right atria [RA]). Oxygenated blood is delivered to the heart from the placenta and travels through the right atrium to the right ventricle and through the PA, where it is shunted across the patent ductus arteriosus (PDA) to the aorta. Only about 10% of the blood traveling through the fetal PA will actually pass through the pulmonary vasculature. Blood is also shunted from the right atrium to the left atrium (a right to left shunt) across the patent foramen ovale (PFO), and then it travels to the aorta and systemic circulation (Reference 89).

At birth, PVR drops because of lung expansion and inhalation of oxygen, a potent pulmonary vasodilator. The placenta is no longer responsible for oxygenation, and when it is removed, SVR increases, thereby increasing left ventricular and left atrial pressure. This increase in pressure, together with increased blood return from the lungs to the left atrium, causes the PFO to close. Closure of the ductus venosus occurs after the termination of umbilical blood flow, which decreases pressure in the inferior vena cava and right atrium. The production of prostaglandin E2 (PGE_2), a potent vasodilator, drops, and the PDA begins to close, with complete closure occurring in about 96 hours. When these shunts have completely closed, the heart is considered to have mature circulation (Reference 89).

Congenital Heart Disease

Patent Ductus Arteriosus

A PDA is the connection between the PA and the aorta, which is necessary to bypass the pulmonary vasculature in utero. The PDA should completely close about 96 hours after birth because of a decrease in endogenous PGE synthesis (References 5, 6, 89) (Figure 3). A PDA that does not close spontaneously accounts for around 10% of all congenital heart disease, and a

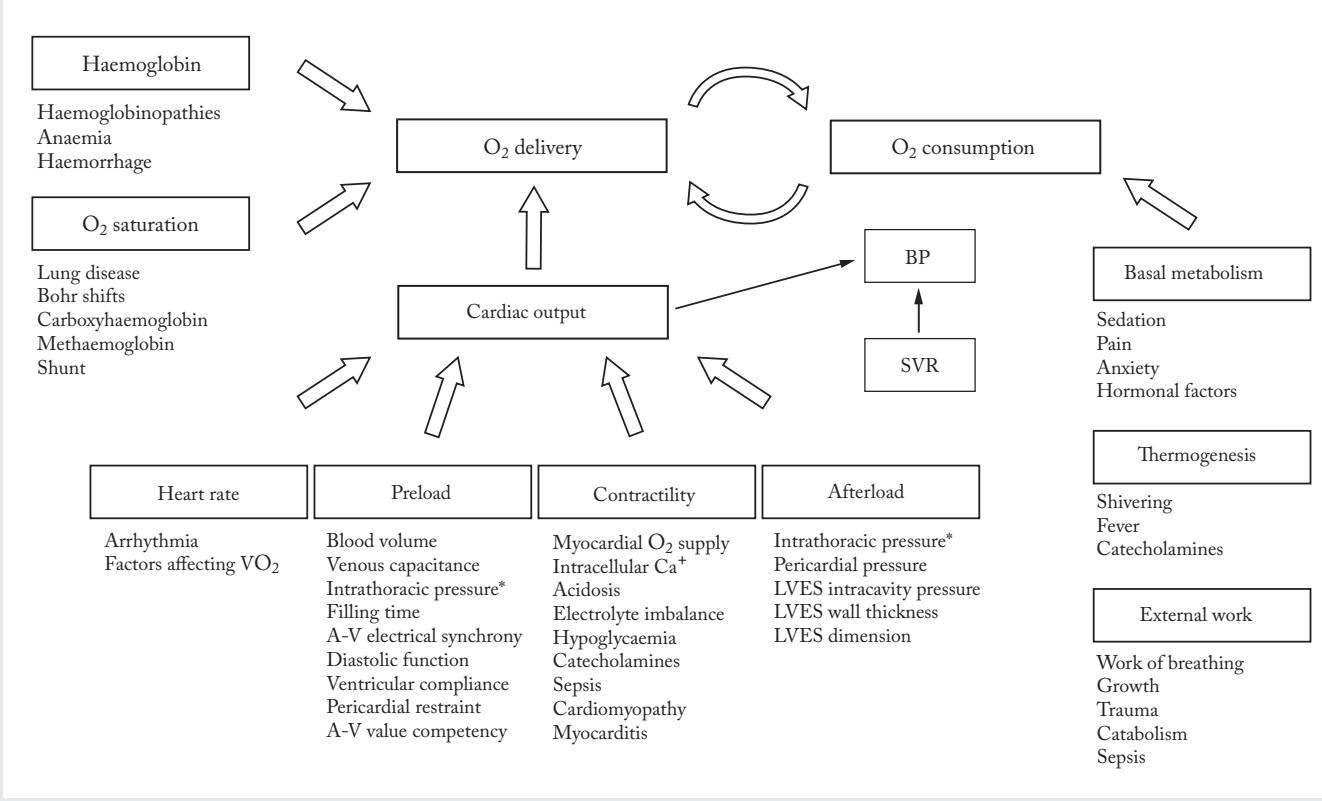


Figure 2. Monitoring of cardiac output.
This figure represents the complicated assessment and treatment of postoperative low cardiac output syndrome for a patient who has undergone surgical repair of a congenital heart defect. The goal of treating low cardiac output syndrome is to improve the delivery of oxygen to end organs, adequately providing tissues with oxygen as needed according to demand. Pharmacologic manipulation of cardiac output focuses on optimizing preload, increasing contractility, and decreasing afterload. A-V (AV) = atrioventricular; BP = blood pressure; LVES = left ventricular end systolic; SVR = systemic vascular resistance.
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PDA will occur in females twice as often as in males (References 1, 2). A PDA will occur as an isolated defect, without other congenital heart disease, in as many as 90% of cases. A PDA occurs more often in premature infants (8 per 1000 births) than in term infants (1 per 5000 births). However, a PDA may be more likely to close spontaneously in a premature infant than in a term infant (References 90–93).

A patient with a PDA will have left to right shunting (from the higher pressure of the aorta to the lower pressure in the PA), resulting in pulmonary overcirculation, congestion, and eventual heart failure or pulmonary hypertension. The degree of symptoms will depend on the size of the PDA, the age at presentation, and the relationship of PVR to SVR. Patients can be given a diagnosis of a PDA on the basis of auscultation, and it can be confirmed with echocardiography. Infants with a PDA may show signs and symptoms of heart failure, including sweating while feeding, tachypnea, poor growth, or cyanosis. Closure of the PDA is important to minimize long-term morbidity and mortality (References 90, 92).

Choice of therapy modality is multifactorial and can depend on the age of the patient, size of the PDA, and other patient-related factors. Nonpharmacologic therapy for a PDA consists of interventional or surgical closure. Interventional closure consists of the insertion of a coil or device into the ductus arteriosus, thus closing it. Morbidity and mortality from this type of procedure is very low, but it requires specialized services (Reference 94). Surgical ligation of the PDA is also an option, typically reserved for patients who do not respond to pharmacologic therapy or those who have very large PDAs.

Before the closure of a PDA, pharmacotherapy is focused on reducing pulmonary congestion, heart failure, and pulmonary overcirculation. Restriction of fluids and use of diuretics is common practice (Reference

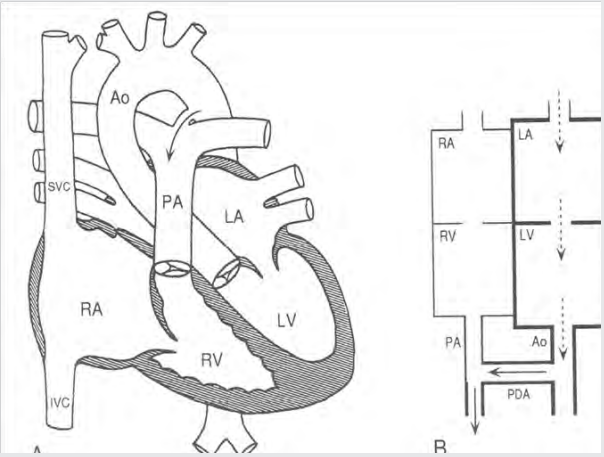


Figure 3. Patent ductus arteriosus.
This diagram represents the anatomic description of a PDA (A) and the movement of blood flow in a patient with a PDA (B). The arrows represent blood shunting from the higher-pressure (left) side to the lower-pressure pulmonary arterial (right) side, resulting in pulmonary overcirculation and congestion.
Ao = aorta; IVC = inferior vena cava; LA = left atria; LV = left ventricle; PA = pulmonary artery; PDA = patent ductus arteriosus; RA = right atria; RV = right ventricle; SVC = superior vena cava.
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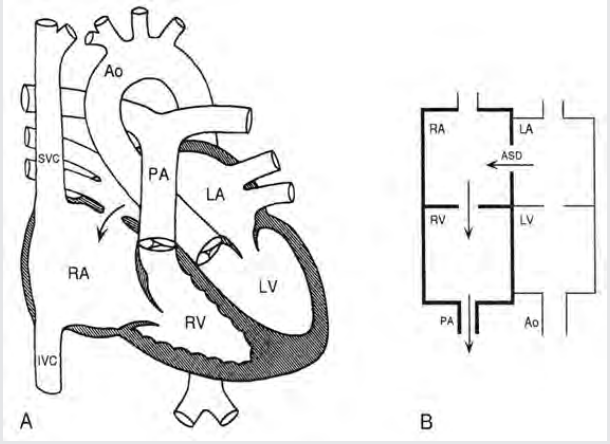


Figure 4. Atrial septal defect.
This diagram represents the anatomic description of an ASD (A) and the schematic movement of blood flow in a patient with an ASD (B). The arrows represent blood shunting from the higher-pressure (left) side to the lower-pressure pulmonary arterial (right) side, resulting in pulmonary overcirculation, congestion, and potential right atrial enlargement.
Ao = aorta; ASD = atrial septal defect; IVC = inferior vena cava; LA = left atria; LV = left ventricle; PA = pulmonary artery; RA = right atria; RV = right ventricle; SVC = superior vena cava.
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90). However, the use of loop diuretics, such as furosemide, should be approached with caution because they have been noted to increase PGE synthesis, thus potentially impairing closure of the PDA (References 95–97). Pharmacologic therapy for closure of a PDA consists of the nonsteroidal anti-inflammatory medications indomethacin (0.2 mg/kg/dose IV initially, with subsequent doses based on post-natal age) or ibuprofen (10 mg/kg/dose IV initially, followed by 5 mg/kg/dose IV at 24 and 48 hours) (Reference 66). By administering these agents, circulating concentrations of PGEs are decreased, thus promoting constriction and closure of the PDA. Intravenous indomethacin has traditionally been the agent of choice for pharmacologic closure of a PDA, and it is given in escalating doses during a 72-hour period. Recent publications have shown a lack of clinically significant differences between intravenous ibuprofen and intravenous indomethacin for closure of a PDA in a term infant, though ibuprofen may have fewer adverse events in preterm neonates, such as lower serum creatinine values and higher urine output (Reference 98). Indomethacin serum concentrations can be evaluated to potentially improve closure rates and minimize adverse events, but not all centers have the capability to perform them (Reference 99). Adverse events associated with indomethacin and ibuprofen therapy include necrotizing enterocolitis, bleeding (including intracranial hemorrhage), and acute kidney injury. After closure of an isolated PDA, long-term survival is excellent, and a normal life span is expected.

Atrial Septal Defect

An atrial septal defect (ASD) is a communication between the RA and LA through the atrial septum (Figure 4). Atrial septal defects comprise about 10% of all congenital heart defects and occur twice as often in females as in males (References 1, 2). Most ASDs occur in the middle of the septum (ostium secundum ASD), but others can occur close to the atrioventricular valves (ostium primum ASD) or close to the superior vena cava (sinus venosus ASD). Oxygenated blood is shunted from left to right into the RA, resulting in pulmonary overcirculation, right atrial enlargement, and, potentially, heart failure. In complicated cases with elevated PVR, blood may actually shunt from the RA to the LA, causing cyanosis (Reference 13). Most patients with an ASD remain asymptomatic, at least

initially, and some ASDs close spontaneously (Reference 100). Right atrial enlargement, caused by volume overload from the left to right shunt, can result in atrial arrhythmias, particularly in older children and adults. Symptomatology is often related to the size of the ASD; large ASDs may have significant shunting and should undergo surgical or interventional closure in the cardiac catheterization laboratory. Interventional closure carries less morbidity than surgical closure, but it can only be performed in select patients. Overall mortality for surgical or interventional closure is very low, and patients can be expected to have a normal life span after their procedure (References 101, 102).

Preoperative pharmacotherapy is limited in patients with ASDs associated with significant shunting because closure of the ASD is the curative course. Relief of symptoms including pulmonary congestion can be achieved with diuretics. Surgical closure of an ASD may require pharmacologic therapy to treat postoperative hypertension, which is not often observed after device closure. Angiotensin-converting enzyme inhibitors, nitroprusside, and β-blockers are all viable options for treating hypertension in the postoperative period. Anticoagulation after surgical or interventional closure is often indicated until endothelialization of the surgical patch or device has occurred. Typically, low-dose aspirin (1–5 mg/kg/day; maximum 81 mg/day) is used for 3–6 months after closure despite limited data on the efficacy of this practice. Patients without comorbidities can be expected to live a normal life span.

Ventricular Septal Defect

A ventricular septal defect (VSD) is a communication between the left ventricle and right ventricle through the ventricular septum, which may occur anywhere along the septum (Figure 5). Ventricular septal defects are the most common congenital heart defect, comprising about 20% to 30% of all congenital heart defects (References 1, 2). Typically, oxygenated blood is shunted from left to right (a "restrictive" VSD), resulting in pulmonary overcirculation, congestion, heart failure, and, possibly, pulmonary hypertension (Reference 13). The degree (and direction) of shunting depends on the size of the VSD and the relationship between PVR and SVR. Patients with pulmonary hypertension may shunt unoxygenated blood from right to left into the systemic circulation. Ventricular septal defects can also occur in combination with other congenital heart defects and may be large enough ("nonrestrictive") to cause cyanosis because of the right to left shunting of unoxygenated blood to the systemic circulation (Reference 13).

Symptomatology is related to the size of the VSD and its associated comorbidities (i.e., pulmonary hypertension). Patients with very small VSDs may be asymptomatic, but otherwise, symptoms may include dyspnea, poor feeding, failure to thrive, or signs and symptoms of heart failure. Patients with a VSD are at increased risk of developing bacterial endocarditis, regardless of VSD size. Diagnosis of a VSD can be made by auscultation, and echocardiography is often used to confirm the diagnosis and determine the size and shunting direction of the VSD (Reference 89).

Surgical closure is the primary method for correction of a VSD, and surgical mortality is very low. However, up to 25% of patients with a VSD have spontaneous closure during childhood, and small VSDs are more likely to spontaneously close than a large VSD (Reference 103). Surgical intervention should take place in neonates and infants with failure to thrive and signs and symptoms of heart failure. In addition, children with pulmonary hypertension, regardless of the size of VSD, should undergo surgical or interventional closure.

The goal of preoperative pharmacotherapy in patients with a VSD is to minimize pulmonary congestion, prevent heart failure, and maintain growth. Various agents have been used to reduce afterload and minimize congestion. Hydralazine was initially the agent of choice, but recently, furosemide (or other diuretics), digoxin, and ACEIs have been used (References 60, 62, 104–108). Caution is warranted when using ACEIs because of the risk of acute kidney injury, particularly in very young patients with a VSD (References 60, 63, 65). Immediate postoperative management consists of maintaining cardiac output and management of postoperative hypertension. Patients may still be hypertensive after discharge and should be followed until resolution. Anticoagulation with aspirin at low doses can be used for 3–6 months after a surgical procedure to help prevent thrombus formation on the VSD patch. Patients without comorbidities can be expected to live a normal life span.

Tetralogy of Fallot

The anatomic description of TOF consists of four components: pulmonary stenosis, aorta overriding the ventricular septum, right ventricular hypertrophy, and VSD (References 5, 6, 89) (Figure 6). Tetralogy of Fallot accounts for about 10% of all congenital heart defects and is the most common cyanotic heart defect in patients younger than 1 year (References 1, 2). The degree and frequency of shunting is based on the severity of the pulmonary stenosis. In patients with mild pulmonary stenosis, shunting can occur from left to right across the VSD and result in heart failure. These patients are often referred to as a "pink tet." In

patients with moderate to severe pulmonary stenosis, blood flow is more limited to the pulmonary vasculature, resulting in desaturation, otherwise known as a "blue tet." Presenting symptomatology in patients with TOF depends on the severity of pulmonary stenosis and the degree of right to left shunting. Neonates may be born with severe pulmonary stenosis that requires immediate surgical intervention. However, older patients may have mild pulmonary stenosis with only occasional symptomatology. Most patients will present within the first year of life, and signs and symptoms can include decreased growth or poor feeding, dyspnea on exertion, or decreased tolerance to physical activity. Older patients will also show signs of clubbing from chronic cyanosis.

When PVR is acutely greater than the pressure in the left ventricle, the shunting of unoxygenated blood from right to left occurs. This is termed a *hypercyanotic episode*, or "Tet spell." Hypercyanotic spells often occur when patients are ill or agitated or when they have been unable to inhale enough oxygen to maintain pulmonary vasodilation (i.e., crying). These are medical emergencies, and interventions are urgently required to shunt blood from left to right and into the pulmonary vasculature (References 109, 110).

Surgical intervention is the curative approach for TOF. The VSD is closed in such a way that the aorta then originates only from the left ventricle. To relieve the PA stenosis, infundibular masses can be resected, the PA can be augmented with a patch, or the PA can be completely replaced with synthetic valved conduit. Former surgical approaches included the preliminary use of a BT shunt, which connects the aorta to the PA, bypassing the stenotic region of the PA, and then moves on to a complete repair later. This approach is no longer used with great frequency unless the patient has specific morbidities that do not allow an immediate complete repair (Reference 13).

Preoperative management consists of minimizing right to left shunting and preventing heart failure. Patients at risk of having a Tet spell are often placed on propranolol, which minimizes the spasm of the infundibulum below the PA and relaxes the right ventricle

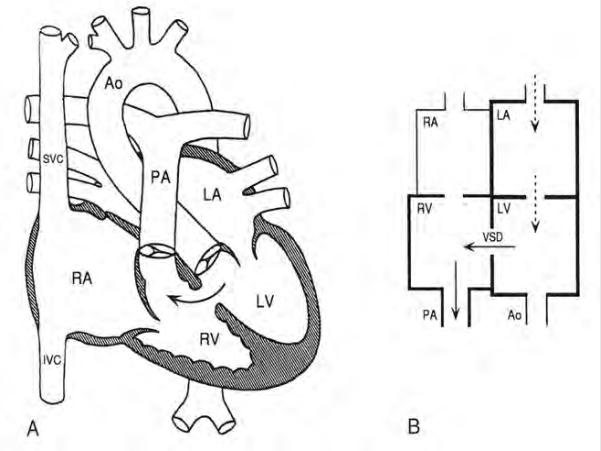


Figure 5. Ventricular septal defect.
This diagram represents the anatomic description of a VSD (A) and the schematic movement of blood flow in a patient with a VSD (B). The arrows represent blood shunting from the higher-pressure (left) side to the lower-pressure pulmonary arterial (right) side, resulting in pulmonary overcirculation, congestion, and heart failure. Left ventricular enlargement can also occur, secondary to increased blood return from the lungs to the LA and LV, resulting in systolic dysfunction and heart failure.
IVC = inferior vena cava; LA = left atria; LV = left ventricle; RA = right atria; RV = right ventricle; VSD = ventricular septal defect.
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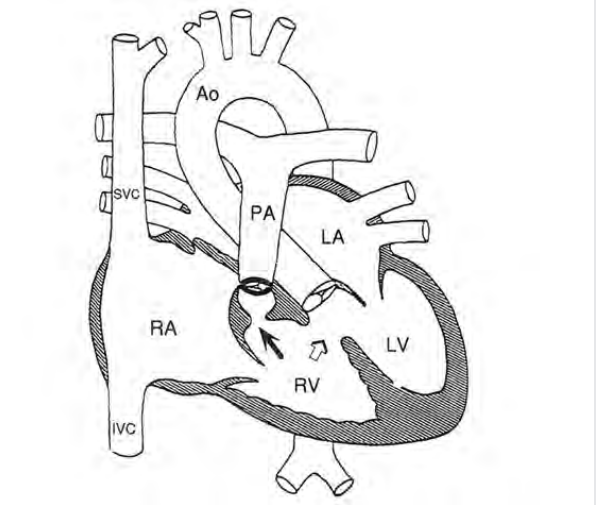


Figure 6. Tetralogy of Fallot.
This figure depicts the four components of tetralogy of Fallot: pulmonary artery stenosis, right ventricular hypertrophy, aorta overriding the ventricular septum, and ventricular septal defect. Patients experience hypercyanotic episodes ("Tet spells") when pulmonary vascular resistance is elevated, and unoxygenated blood is shunted from right to left and to the systemic circulation.
Ao = aorta; IVC = inferior vena cava; LA = left atria; LV = left ventricle; PA = pulmonary artery; RA = right atria; RV = right ventricle.
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and right ventricular outflow tract (References 111, 112). Treatment of a Tet spell focuses on elevating SVR and decreasing PVR. Older patients may have a characteristic known as "squatting" in response to a Tet spell, also referred to as the "knee-to-chest maneuver" (References 62, 108). By bringing the knees to the chest, SVR is increased, left ventricular pressure is increased, and blood is shunted from left to right. Pharmacologic interventions include oxygen (decreases PVR), morphine (decreases PVR), fluids (increases right ventricular filling and pulmonary blood flow), β-blockers, and intravenous phenylephrine (increases afterload).

Immediate postoperative management consists of maintaining cardiac output, treating postoperative hypertension, and ensuring adequate pulmonary blood flow. Inhaled nitric oxide has been used to improve pulmonary blood flow after surgical correction (Reference 113). Patients are often given low-dose aspirin for 3–6 months after placement of foreign material, such as a PA patch, or patients may take aspirin indefinitely if a pulmonary valve has been placed (Reference 114).

Long-term management of surgically corrected TOF focuses on prevention and treatment of heart failure, treatment of right ventricular dysfunction, and treatment of arrhythmias. The long-term survival for patients with surgically corrected TOF is good (estimated at 86% at older than 30 years), but it is still less than that for patients without congenital heart disease (Reference 1).

Transposition of the Great Arteries

Transposition of the great arteries (TGA) is a defect in which the PA arises from the left ventricle, and the aorta arises from the right ventricle (Figure 7). This defect accounts for about 7% of all congenital heart defects, and it is diagnosed in infancy (References 1, 2). Patients may or may not have a VSD in conjunction with TGA. In utero, patients have a communication between the PA and aorta by the PDA and PFO. After birth, the PDA and PFO begin to close, and the patient can develop profound acidosis and shock caused by the lack of oxygenated blood flowing to end organs. Patients can be given diagnoses prenatally through fetal echocardiography, but often, they present in shock about 24–72 hours after birth, when the PDA begins to close. Echocardiography after birth can definitively diagnose TGA.

Surgical correction by the arterial switch procedure is the standard for patients with TGA. Surgery should occur in the first 1–2 weeks of life so that the left ventricle (which would be currently pumping to the pulmonary vasculature) does not become deconditioned and can handle the stress of pumping to a systemic circulation (References 13, 89). The arterial switch procedure consists of removing the PA and the aorta and placing them in the appropriate location. In addition, the coronary arteries that were coming off the PA (in place of the aorta) are removed and reattached to the aorta in its new position. Before the arterial switch procedure, the Mustard procedure, which consisted of a complex series of intracardiac baffles to shunt blood to the appropriate vessels, was a common surgical approach. Patients with TGA in combination with pulmonary stenosis may still undergo the Mustard procedure to avoid placing the stenotic PA in the aortic position (Reference 116).

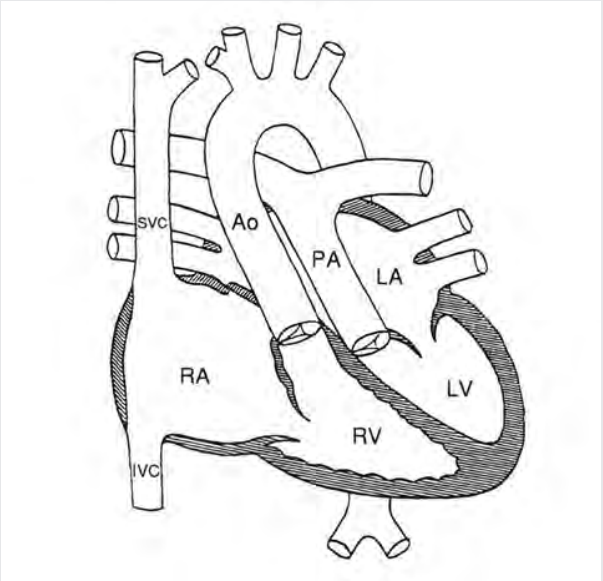


Figure 7. Transposition of the great arteries.
This diagram represents the anatomy of TGA, in which the aorta (Ao) arises from the right ventricle (RV), and the pulmonary artery (PA) arises from the left ventricle (LV). In utero, the PDA would connect the Ao and PA. After birth, once the PDA begins to constrict, two separate circulations form in the patient with TGA. (1) Unoxygenated blood travels from the IVC/SVC → RA → RV → Ao → systemic circulation without going to the pulmonary vasculature. (2) Oxygenated blood travels from the pulmonary veins → LA → LV → PA → lungs without going to the systemic circulation. In summary, oxygenated blood never reaches the end organs, and unoxygenated blood is continually recycled through the systemic circulation.
IVC = inferior vena cava; LA = left atria; PDA = patent ductus arteriosus; RA = right atria; SVC = superior vena cava; TGA = transposition of the great arteries.
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Preoperative pharmacotherapy of TGA consists of maintaining the PDA to ensure that oxygenated blood flows from the PA to the aorta. This is accomplished by using a prostaglandin E1 (PGE_1) infusion to maintain ductal patency (Reference 117). Immediate postoperative pharmacotherapy should manage LCOS. Patients may also be placed on a prophylactic nitroglycerin infusion, as a coronary vasodilator, to prevent coronary vasospasm after their surgical manipulation. Long-term pharmacotherapy is minimal because patients should have normal circulation, and long-term survival for patients after the arterial switch procedure is good, cited at about 85% (References 118, 119).

Coarctation of the Aorta

A patient with coarctation of the aorta has a narrowing of the aorta, which restricts blood flow to the systemic circulation (Figure 8). Aortic coarctations are often associated with other congenital heart defects and account for about 6% of all congenital heart defects. Coarctations are also typically divided into two categories: preductal and postductal (References 1, 2). Preductal coarctation occurs most often in a fetus with another cardiac anomaly that restricts blood flow to the aorta and is associated with aortic arch hypoplasia. Postductal coarctation occurs most often after birth, as an isolated lesion, and is most likely the result of ductal tissue in the aorta that constricts after birth (References 13, 89). Both forms of coarctation can result in decreased cardiac output and left ventricular hypertrophy because of the aortic obstruction.

Neonatal patients with preductal coarctation can exhibit differential cyanosis (differing oxygen saturations on the upper and lower parts of the body) because of unoxygenated blood shunting from the PA through the PDA to the aorta. Coarctations can also cause differential blood pressures based on the location of the coarctation in relation to the ductus (i.e., if the ductus is after the subclavian arteries, blood pressure will be higher in the arms than in the legs). Neonates with severe coarctation will present in shock with profound acidosis, caused by lack of blood flow to end organs (References 13, 89). Less severe forms can present with tachypnea, hepatomegaly, dyspnea, and tachycardia. Some patients with mild coarctation may never experience any symptomatology and may grow and develop normally. Collateral arteries may develop spontaneously in some patients to accommodate for the lack of blood flow through the aorta, and these collateral arteries can erode through the ribs (References 13, 89). A coarctation may be diagnosed in older patients who experience dyspnea on exertion or syncope. Echocardiography or magnetic resonance imaging can be used to confirm the diagnosis (References 13, 89).

Surgical correction is necessary to eliminate the coarctation. Two surgical methods are commonly employed: end-to-end anastomosis or patch repair. The end-to-end anastomosis does not involve cardiopulmonary bypass and can occur when the coarctation does not involve the carotid arteries. During this procedure, both ends of the coarctation are clamped, the narrowed section is dissected, and the aorta is then sutured together. The patch repair technique involves cardiopulmonary bypass, the coarctation is dissected, and the aorta is repaired with a prosthetic patch. Operative mortality is very low, reported at less than 2%, but it can be higher in neonates presenting in shock (Reference 13).

Preoperative pharmacotherapy is aimed at maintaining cardiac output in the presence of an obstruction. For preductal coarctations, PGE_1 may be used to maintain the PDA and deliver systemic blood flow postductus (Reference 117). Managing heart failure and decreasing afterload are also strategies for maintaining cardiac output before surgical intervention. In the immediate postoperative period, many patients

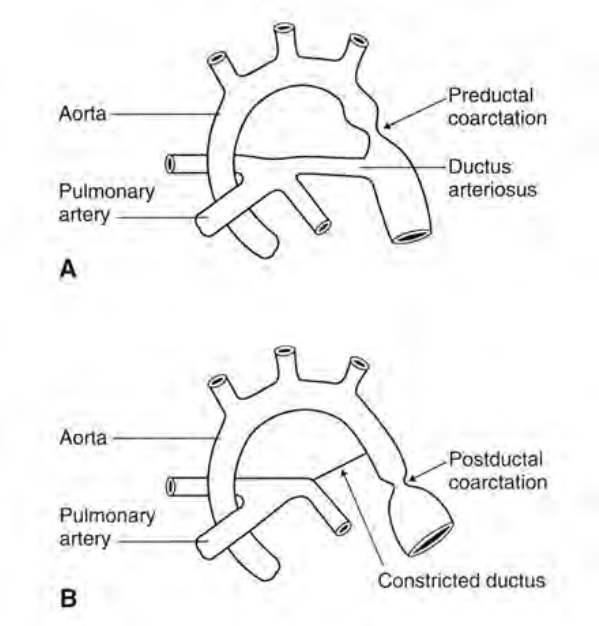


Figure 8. Coarctation of the aorta.
These diagrams represent two versions of coarctation of the aorta. A coarctation can occur before the ductus arteriosus (A) or after the ductus arteriosus (B). In addition, the preductal coarctations can occur further up the aortic arch and involve the carotid or subclavian arteries.
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experience hypertension after coarctation repair (Reference 117). The etiology of this hypertension is not completely understood, but it should be managed appropriately to avoid rupturing aortic sutures. Many agents have been used, including esmolol, nitroprusside, labetalol, enalaprilat, and nicardipine (References 43, 120–127). Long-term management of hypertension is necessary for up to 6 months after the surgical procedure. Patients should be followed routinely because there is a potential for re-coarctation. The long-term survival rate for patients with coarctation repair is excellent.

Hypoplastic Left Heart Syndrome

Patients with hypoplastic left heart syndrome (HLHS) have a small to nonexistent left ventricle and narrow (or atretic) aorta (Figure 9). Patients are unable to survive with HLHS without treatment because of insufficient blood flow from the left ventricle through the aorta to the systemic circulation. Hypoplastic left heart syndrome represents only about 1% of all congenital heart defects, but HLHS uses the largest amount of resources compared with other congenital cardiac defects (References 1, 2). Hypoplastic left heart syndrome is not compatible to life, but because of intracardiac shunting as a fetus, infants may not be given a diagnosis until they present postnatally in shock as the PDA begins to close.

This condition was uniformly fatal before the early 1980s, when Dr. William Norwood introduced the three-stage approach to surgical repair of HLHS (Reference 128). Before initial surgical intervention, patients may require a balloon atrial septostomy to create an ASD if the PFO has closed or is too small. The ASD allows shunting of oxygenated blood from the LA to the RA, which is necessary for survival. The first stage of the surgical palliation occurs within the first few days of life and includes the following procedures: combining the aorta and PAs into one "neo-aorta" (also called the Damus-Kaye-Stansel procedure), creating a large ASD, and placing an aortopulmonary shunt, also known as the BT shunt. These interventions allow oxygenated blood from the lungs to flow from the pulmonary veins to the LA, across the septum to the RA (where it mixes with deoxygenated blood from the inferior vena cava/superior vena cava), to the right ventricle. Blood then flows through the neoaorta and then either to the lungs (by the BT shunt) or the systemic circulation by the aorta. Modifications of this initial stage have occurred with the Sano procedure, which replaces the BT shunt with a right ventricle to PA conduit (Reference 129). Hybrid procedures have been performed that involve stenting the PDA open to supply blood flow to the aorta from the PA, together with banding of the branch PAs, which restricts pulmonary blood flow and prevents overcirculation (References 130–132). Because there is complete mixing of oxygenated and unoxygenated blood at the atrial level, oxygen saturations after the Norwood and associated procedures should be at about 70% to 80%. This represents an equal amount of blood flow to the pulmonary and systemic circulations (a Qp/Qs ratio of 1:1) (Reference 13).

The second stage of the palliation, the bidirectional Glenn procedure, occurs at 4–6 months of life and removes the BT shunt from the earlier Norwood procedure and attaches the superior vena cava to the PA (Reference 133). This delivers a greater amount of blood flow to the pulmonary vascular bed, and oxygen saturations generally increase to about 80% to 85% (Reference 13).

The Fontan procedure is the final stage of palliation, which consists of attaching the inferior vena cava, through a conduit, to the PA (Reference 134). This procedure occurs at about age 3 years and completely separates the pulmonary and systemic circulations. The separated circulations should allow oxygen saturations to return to normal (95% to 100%) with a single right ventricle pumping for both pulmonary and systemic circulations. A small fenestration is usually created between the conduit and the right atrium to relieve pressure in the conduit if the PVR becomes too high (Reference 13).

Preoperative pharmacotherapy for HLHS before the Norwood procedure consists of maintaining the PDA to ensure blood flow through the aorta to the systemic circulation with PGE_1 administration, as well as managing the signs and symptoms of heart failure (References 135, 136). Prostaglandin E1 infusions are titrated to the lowest possible dose that will maintain ductal patency and minimize adverse events, such as hypotension or apnea. In the immediate postoperative period, treatment of LCOS and balancing of systemic and pulmonary blood flow are the goals of cardiovascular pharmacotherapy. Patients are often anticoagulated with a low-dose heparin infusion (6–10 units/kg/hour) until they are able to receive enteral medications; then, low-dose aspirin (1–5 mg/kg/day) is used as an antiplatelet agent for the prevention of BT shunt thrombosis (Reference 137). The ideal long-term, or inter-stage, management strategy for patients after a single ventricle palliation is unclear (References 138, 139). Sudden death during the inter-stage period can occur, and an exact etiology for this phenomenon is unknown (Reference 140). In addition, the lack of inter-stage weight gain has been noted for patients after single ventricle palliation, which has been thought to contribute to mortality (References 141–143). Pharmacotherapy has elicited few improvements in this area, with recent publications showing

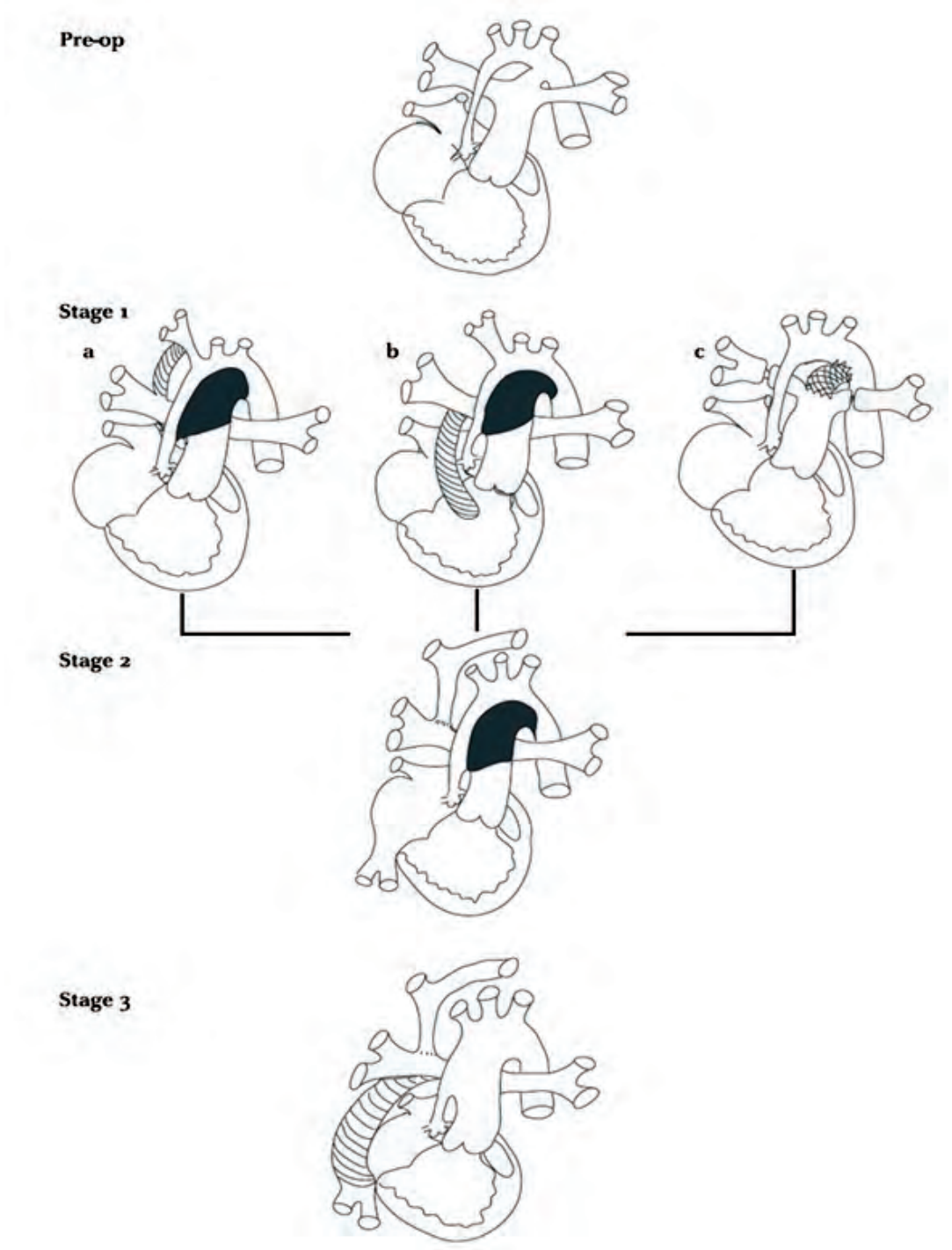


Figure 9. Hypoplastic left heart syndrome and three-stage surgery.
This diagram represents the anatomy of unrepaired hypoplastic left heart syndrome (HLHS). Note the aortic atresia and small left ventricle. Stage 1 represents three options for the initial palliation of HLHS. (a) The classic Norwood procedure combines the aorta and pulmonary artery (also known as the Damus-Kaye-Stansel procedure), creation of an atrial septal defect, and placement of a Blalock-Taussig (BT) shunt. (b) The Sano procedure replaces the BT shunt with a right ventricle to pulmonary artery conduit. (c) A hybrid procedure involves stenting of the ductus arteriosus and banding of the branch pulmonary arteries. Stage 2 is the bidirectional Glenn procedure, in which the BT shunt or right ventricle to pulmonary artery conduit is taken down, and the superior vena cava is attached to the pulmonary artery. Stage 3 is the Fontan procedure, in which an extracardiac conduit is used to attach the inferior vena cava to the pulmonary artery, subsequently dividing pulmonary and systemic circulations.
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the ineffectiveness of ACEIs and other medications in improving inter-stage weight gain (Reference 7). Current best practice appears to be close monitoring of weight and frequent follow-up before the bidirectional Glenn (References 141–143).

Little information exists for the pharmacotherapeutic management of the patient after the bidirectional Glenn procedure. Immediate postoperative management consists of maintaining cardiac output and preventing thrombus with a low-dose heparin infusion (6–10 units/kg/hour). Anecdotally, a nitroglycerin infusion has been used to help maintain the patency of the superior vena cava to PA anastomosis. Long-term pharmacotherapy in patients after the bidirectional Glenn is directed toward the prevention of heart failure and the maintenance of adequate cardiac output.

Immediate postoperative management of the patient after the Fontan procedure is focused on maintaining cardiac output and preventing LCOS. Patients are at risk of developing pleural or chylous effusions after the Fontan procedure. Literature has shown variable efficacy in restricted fat intake and the use of octreotide to decrease chylous effusions (References 144–146). Protein-losing enteropathy (PLE) can also occur in post-Fontan patients. Treatment of PLE has consisted of subcutaneous heparin injections, even though the mechanism for the benefit of this therapy is unclear (Reference 147). Recent literature has shown that the use of enteral budesonide or octreotide may be useful in the treatment of PLE after the Fontan procedure (References 148, 149).

One of the most controversial areas in pharmacotherapy for the Fontan patient is anticoagulation. Because of the physiology and hemodynamics of the Fontan circuit, the RA can become enlarged, with patients potentially developing atrial arrhythmias, such as atrial fibrillation or atrial flutter, leading to thrombus formation. Several studies have evaluated the risks and benefits of aspirin anticoagulation compared with warfarin anticoagulation in the Fontan patient without arrhythmias, finding that bleeding risk is increased with warfarin, but thrombus formation is increased with aspirin use (References 150–154). If a patient does develop atrial arrhythmias, warfarin is most likely indicated to prevent thrombus formation (References 114, 155). Currently, no consensus exists for the optimal anticoagulation regimen for a patient after the Fontan procedure.

Long-term pharmacotherapeutic management of the Fontan patient includes the prevention and management of heart failure. There is currently no consensus on the optimal management or prevention of heart failure in a patient with a single right ventricle, and practice varies widely (Reference 5). In addition, heart failure in this population differs significantly from that in other adult populations because heart failure in the Fontan is caused by pressure/volume overload in a right ventricle. Enalapril and sildenafil have been studied in Fontan patients, but neither has been shown to improve symptoms or exercise tolerance (References 156–159). β-Blockers may show some benefit in failing Fontan, but large trials have not been performed (References 160, 161). Further research in this area is warranted to improve long-term outcomes.

Because the Fontan procedure is the terminal operation in the staged repair of HLHS, patients can develop several complications throughout their lifetime. Many patients undergo revisions of their original Fontan circuit because of decreased exercise tolerance or increasing cyanosis. Life expectancy and quality of life have improved with time. As surgical and medical management continues to improve, patients will live longer, and health care providers will require specialized training and knowledge to appropriately care for patients with a single ventricle.

Future Directions

As surgical and medical management of congenital heart disease in children improves, patients are surviving into adulthood. The population of adult patients with congenital heart disease is growing by 5% per year, representing well over 1 million patients in the United States alone (References 162–164). Management of the adult patient with congenital heart disease is an area that requires clinicians to have specialized knowledge in both pediatric and adult cardiovascular diseases. Morbidity can be high in this patient subset, and currently, few centers are developed to care for this patient population (References 165, 166). The unique cardiac pathophysiologies and comorbidities in this patient population make application of pharmacotherapy challenging and ripe for research and evaluation (Reference 167). In addition, the neurologic complications that can be associated with cardiopulmonary bypass, chronic cyanosis, and low-flow states are undergoing evaluation. It is well known that patients with congenital heart disease can have lower levels of cognitive function, and future directions include research to eliminate this morbidity (References 168–172).

Conclusions

The pharmacotherapeutic management of patients with congenital heart disease is complex and plagued by a lack of data compared with that for adult patients with cardiac pathophysiology. A comprehensive understanding of pathophysiology, hemodynamics, and pediatric pharmacology is necessary to optimize outcomes for this challenging patient population.

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CHAPTER 10

Pediatric Arrhythmias

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Learning Objectives

1. Understand the epidemiology and pathophysiology of common pediatric arrhythmias.
2. List pharmacologic options for the acute and chronic treatment of common pediatric arrhythmias.
3. Identify monitoring parameters for therapeutic efficacy and toxicity for pharmacotherapy of common pediatric arrhythmias.

Abbreviations in This Chapter

AVNRT	Atrioventricular nodal reentrant tachycardia
AVRT	Atrioventricular reentrant tachycardia
ECG	Electrocardiogram/electrocardiographic/electrocardiography
LQTS	Long QT syndrome
PJRT	Permanent junctional reciprocating tachycardia
SVT	Supraventricular tachycardia
TdP	Torsades de pointes
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White (syndrome)

Introduction

This chapter will focus on arrhythmias common to the pediatric population, divided into three major subsections: supraventricular tachyarrhythmias, ventricular tachyarrhythmias, and bradyarrhythmias. Our goal is to have these three sections encompass most management strategies for arrhythmias seen by a pediatric pharmacist evaluating drug therapy for pediatric patients. However, there will be exceptions to the strategies presented, particularly for those practicing in large, tertiary referral centers, and the reader will be given references for further investigation of uncommon arrhythmias.

Some assumptions were made when writing this chapter. Because this textbook focuses on the pediatric age group, only aspects of arrhythmia pathophysiology, medical care, or pharmacotherapy that are unique to the pediatric population will be discussed. Because of space limitations and the availability of other excellent resources, basic cardiovascular anatomy and physiology (including an in-depth discussion of the mechanism of cardiac conduction) will not be covered in this chapter. Similarly, a basic understanding of electrocardiographic (ECG) interpretation will be assumed. If readers would like an update on these aspects of cardiovascular anatomy and physiology, they are directed to other sources (References 1, 2).

Normal Conduction

The cardiac conduction system consists of the sinoatrial (SA) node, the atrioventricular (AV) node, the bundle of His with the left and right bundle branches, and the Purkinje fibers. In a normal heart, electrical impulses are generated in the SA node and are subsequently transmitted through the atria to the AV node, bundle of His, and left and right bundle branches to the Purkinje fibers, which finally stimulate myocardial contraction.

The basis of electrical conduction begins with the shifting of ions into and out of cells, thus generating a change in polarization, also known as the action potential. The action potential involves four phases, with specific ions involved in each phase (Figure 1). Developmentally, changes in ion transport channels appear to occur with age, leading to increased expression of potassium and calcium channels with older age (Reference 3). In addition, the electrophysiologic characteristics of the AV node have been noted to change in pediatric patients as they age (Reference 4). Although the impact of this on the pharmacotherapy for pediatric arrhythmias is currently unknown, it may be elucidated in the future.

Antiarrhythmic Medications

Antiarrhythmic medications affect ion transport in myocardial cells. Three primary modes of electrical signal transduction and generation are affected: (1) automaticity (the rate of action potential generation), (2) conduction velocity (the speed of action potential movement through the myocardium), and (3) refractory period (the time to repolarize). All antiarrhythmic medications are classified by Vaughan-Williams categories on the basis of their primary mechanism of action (Table 1). The dosing and monitoring of these agents is often individualized on the basis of the arrhythmia being treated and other patient comorbidities

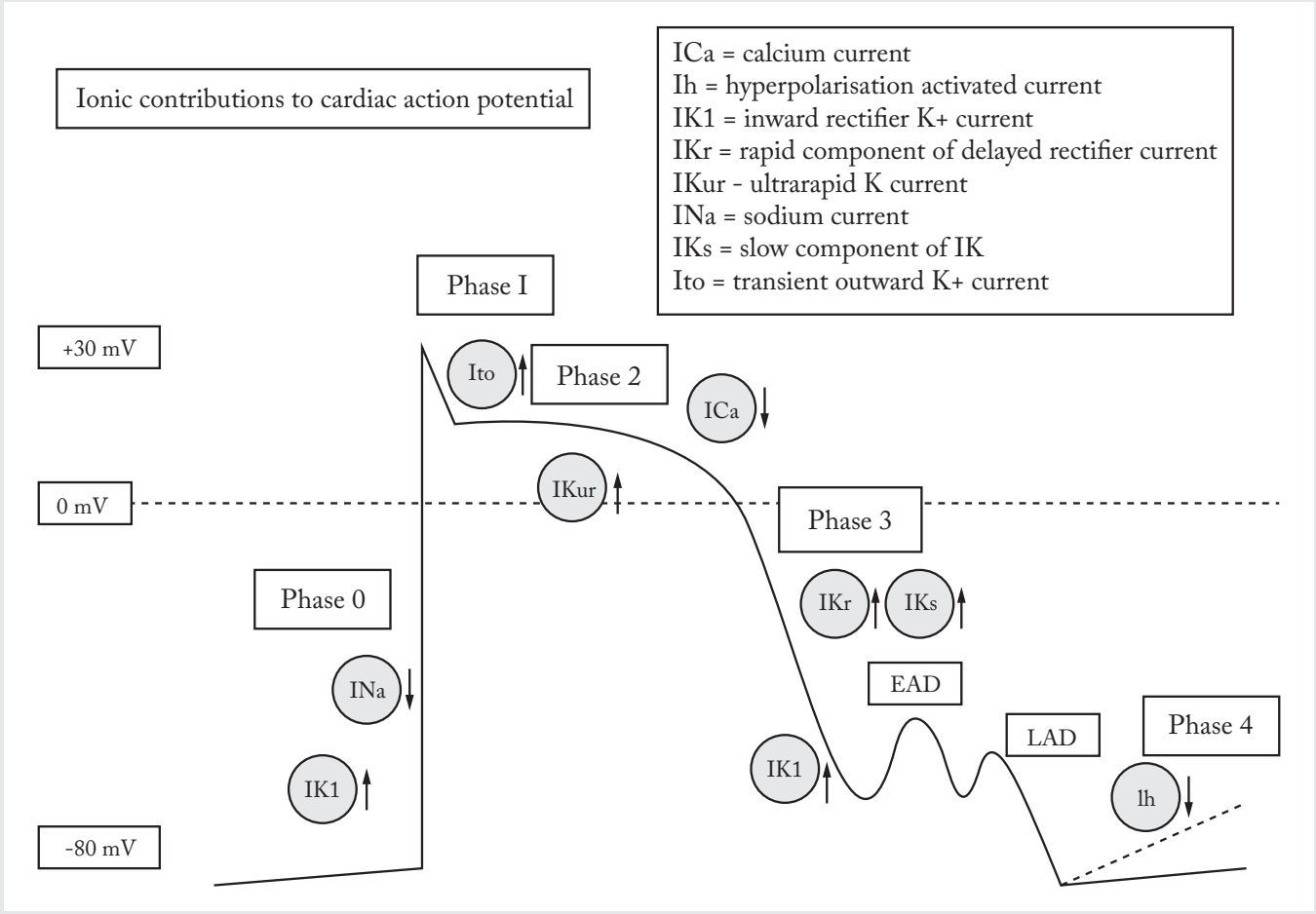


Figure 1. Action potential.

This figure describes the action potential of the Purkinje fibers and the associated ion shifts. Phase 0 consists of Na^+ influx into the cell, resulting in a positive charge. At phase 1, K^+ effluxes from the cell, followed by Ca^{++} ions. K^+ ions efflux from the cell in phase 2. Phase 3 includes more K^+ efflux from the cell, to decrease the action potential threshold. Phase 4 spontaneous depolarization occurs only in pacemaker cells. Early afterdepolarizations (EAD) and late afterdepolarizations (LAD) represent "extra" depolarizations that can occur in patients with prolonged phase 2 and phase 3 (K^+ channel) repolarizations, potentially resulting in arrhythmias. Republished with permission from Chakrabarti A, Stuart AG. Understanding cardiac arrhythmias. Arch Dis Child 2005;90:1086–90.

(Reference 5). In addition, the effect of each of these medications on electrophysiologic and hemodynamic parameters has been summarized. Each of these drugs will be evaluated in depth regarding their effect on various arrhythmias in the upcoming sections.

Supraventricular Tachyarrhythmias

Supraventricular tachyarrhythmias are the most common arrhythmia in childhood, occurring in about 1 in every 250 children. A higher prevalence has been reported in patients who have undergone cardiac surgery or have congenital heart disease (Reference 6). However, most patients with supraventricular tachyarrhythmias have structurally normal hearts, and patients are not uncommonly given a diagnosis on routine office visits (Reference 7). Most supraventricular tachyarrhythmias are paroxysmal (lasting 30 seconds or less), but they can be incessant, resulting in significant hemodynamic compromise and heart failure in as little as 24–48 hours (Reference 8). Patients can become symptomatic, exhibiting signs of heart failure such as poor feeding, sweating, and tachypnea in infants and fatigue, tachypnea, and peripheral edema in older patients (Reference 8). Although overall mortality from supraventricular arrhythmias is low, rapid diagnosis and appropriate treatment are essential to minimize patient morbidity (Reference 9).

Overall, supraventricular tachyarrhythmias have been traditionally defined as an abnormally rapid heart rhythm originating above the bundle of His (Reference 10). Within this broad heading, there are many different pathophysiologic mechanisms of arrhythmias, including those with focal atrial tachycardias (FATs),

Table 1. Summary of Antiarrhythmic Medication Dosing in Pediatric Patients (Reference 5)

Drug	Dosage	Notes on Pharmacotherapy
Class Ia (Na^+ channel blockade – moderate)		
Quinidine sulfate	Oral: 30 mg/kg/day or 900 mg/m^2/day given in five daily doses Range: 15–60 mg/kg/day in four or five divided doses IV: 2–10 mg/kg/dose every 3–6 hours as needed (IV not routinely recommended)	Two forms available (sulfate and gluconate). Drug level monitoring typically not performed
Procainamide	IV: Loading dose: 3–6 mg/kg/dose; max 100 mg/dose. May be repeated to a total max of 15 mg/kg IV: Continuous infusion: 20–80 mcg/kg/minute	Procainamide and NAPA concentrations used to guide therapy
Disopyramide	Oral: • < 1 year: 10–30 mg/kg/day in four divided doses • 1–4 years: 10–20 mg/kg/day in four divided doses • 4–12 years: 10–15 mg/kg/day in four divided doses • 12–18 years: 6–15 mg/kg/day in four divided doses	Drug level monitoring typically not performed
Class Ib (Na^+ channel blockade – mild)		
Lidocaine	IV: Bolus: 1 mg/kg/dose IV: Continuous infusion: 20–50 mcg/kg/minute	Drug level monitoring useful for guiding therapy
Mexiletine	Oral: 1.4–5 mg/kg/dose every 8 hours	
Class Ic (Na^+ channel blockade – strong)		
Flecainide	Oral: Starting dose: 1–3 mg/kg/day or 50-100 mg/m^2/day divided three times/day. Max: 8 mg/kg/day or 200 mg/m^2/day. Average effective dose: 4 mg/kg/day or 140 mg/m^2/day	Drug level monitoring useful for guiding therapy
Propafenone	Oral: 200–300 mg/m^2/day divided three or four times/day. Max: 600 mg/m^2/day divided three or four times/day	Drug levels not typically performed
Class II (β-blockade)		
Propranolol	Oral: Neonates: 0.25 mg/kg/dose every 6 hours. Max: 5 mg/kg/day Oral: Infants and children: 0.5–1 mg/kg day in divided doses every 6–8 hours Usual dose: 2–4 mg/kg/day. Max: 60 mg/day	
Esmolol	IV: Bolus: 100–500 mcg/kg/dose IV: Continuous infusion: 300–1000 mcg/kg/minute	
Atenolol	Oral: 0.5–1 mg/kg/day given one or two times/day. Max: 2 mg/kg/day or 100 mg/day	
Metoprolol	Oral: Children 1–17 years: 1–2 mg/kg/day given twice daily. Max: 6 mg/kg/day or 200 mg/day	Extended-release tablets given once daily
Nadolol	0.5–1 mg/kg/day given daily. Max: 2.5 mg/kg/day	
Class III (K^+ channel blockade)		
Sotalol	Oral: Children ≤ 2 years: 30 mg/m^2/dose every 8 hours adjusted per age nomogram OR 2 mg/kg/day divided every 8 hours OR 80–200 mg/m^2/day divided every 8 hours Oral: Children > 2 years: 80–200 mg/m^2/dose divided every 8 hours	Institutional practices for dosing sotalol can vary. ECG monitoring is important for QT-interval prolongation.
Amiodarone	IV: Bolus: 5 mg/kg/dose up to 15 mg/kg. Max dose will vary on the basis of indication. IV: Continuous infusion: 10–20 mg/kg/day or 5–15 mcg/kg/minute Oral: 10–20 mg/kg/day or 600–800 mg m^2/day one or two times/day	Patients may be loaded for 1–2 weeks at the beginning of therapy because of the long half-life of amiodarone. Reduction to the most effective dose can occur after loading.

Class IV (Ca^{++} channel blockade)		
Verapamil	IV: Children 1–15 years: 0.1–0.3 mg/kg/dose. Max: 5 mg/dose Oral: 4–8 mg/kg/day in three divided doses OR 1–5 years: 40–80 mg every 8 hours > 5 years: 80 mg every 6–8 hours	IV use is not recommended in patients < 1 year.
Diltiazem	Oral: Children: 1.5–2 mg/kg/day in three or four divided doses. Max: 8 mg/kg/day	Extended-release formulations can be given once daily.
Digoxin	Oral and IV: Loading doses and maintenance doses have considerable variation depending on age, and dosing information cannot be summarized in the space provided. Historically, oral maintenance doses have ranged from 5 mcg/kg/day to 10 mcg/kg/day divided one or two times/day.	Drug level monitoring usually useful only in assessment of toxicity
Adenosine	IV: 0.1 mg/kg/dose; subsequent doses 0.2 mg/kg/dose, up to 0.3 mg/kg/dose	Administer by rapid push with a rapid flush through intravenous access closest to the heart.

IV = intravenous; max = maximal; NAPA = *N*-acetyl procainamide.

reentrant mechanisms mediated by an accessory pathway outside the AV node (Wolff-Parkinson-White syndrome [WPW] and concealed pathways, permanent junctional reciprocating tachycardia), a reentrant mechanism within the AV node (atrioventricular nodal reentrant tachycardia [AVNRT]), or junctional ectopic tachycardias (JETs). More than 90% of the supraventricular arrhythmias diagnosed in children have a reentrant mechanism, and these will be addressed in the most detail (Reference 11). Typically, the definition of supraventricular tachyarrhythmias excludes atrial fibrillation and atrial flutter, but for completeness, both will be addressed in this section as arrhythmias that are generated above the ventricles.

Initial Management of Supraventricular Arrhythmias

Initial management of supraventricular arrhythmias, before definitive diagnosis, has standard approaches. Vagal maneuvers, such as ice to the face or carotid massage, have been performed for initial management in hemodynamically stable patients with limited success (Reference 12). Initial pharmacologic management often consists of adenosine as a diagnostic and therapeutic tool, causing temporary AV block, depending on the mode of tachycardia (References 13, 14). Despite the widespread use of adenosine for initial management and therapy for supraventricular arrhythmias, proarrhythmic effects have occurred, and defibrillation equipment should be readily available when adenosine is administered (Reference 15).

Focal Atrial Tachycardias

Focal atrial tachycardias, consisting primarily of automatic atrial ectopic tachycardias, account for 4% to 14% of all supraventricular arrhythmias in children and are typically refractory to pharmacologic management (References 16, 17). Although most forms of supraventricular tachyarrhythmias are reentrant in nature, FATs consist of a site within the myocardium that exhibits pacemaker cell characteristics, generating action potentials from areas other than the SA or AV node. Various other forms of FATs can occur, including microreentrant atrial tachycardia, chaotic atrial tachycardia, or multifocal atrial tachycardia (References 11, 18). Patients who have undergone cardiac surgery are often the most likely patient subset for FATs, though some FATs are caused by other disease states or are idiopathic (Reference 16). Patients with FATs will present with an elevated heart rate, typically greater than 200 beats/minute for infants and children. The ECG findings for FATs can be difficult to identify, particularly in patients with heart failure or in neonates (Reference 19). Electrocardiographic readings will show an elevated heart rate with normal QRS and an extended R-P interval, although it may be difficult to see P waves in this type of tachycardia (References 16, 19). The clinical course of FATs can vary depending on age (References 16, 20, 21). Ventricular dysfunction and heart failure can ensue if FATs are not corrected in a timely manner (Reference 22). Catheter ablation may be necessary as a nonpharmacologic intervention for incessant FATs refractory to medical therapy (Reference 23).

The goals of pharmacotherapy for FATs are to decrease the automaticity of the ectopic focus, potentially decrease the conduction velocity of the impulse through the Purkinje fibers, and slow the ventricular rate. Pharmacologic management of FATs, after diagnosis, is based primarily on case-series data, and approaches to treatment vary widely (References 16, 20, 21). Historically, digoxin and class Ia and class IV antiarrhythmic agents have been employed to control FATs, with little effectiveness (References 16, 23, 24). β-Blockers are the most common first-line antiarrhythmic agent. The use of β-blockers such as propranolol or atenolol, with or without digoxin, has had varying results on the effectiveness of control, with some reports showing resolution of arrhythmia, but others showing lack of effect (References 16, 24, 25). Oral propafenone, a class Ic antiarrhythmic, has shown promise for the treatment of FATs, with reported arrhythmia resolution rates from 33% to 89%, although it is not often used at most pediatric centers (References 26–29). It has been hypothesized that patients younger than 1 year without structural heart disease have a better response to propafenone for control of FATs (Reference 30). Another class Ic antiarrhythmic, flecainide, has also been shown to be effective for the treatment of patients with FATs and is more commonly used than propafenone, but it is contraindicated in patients with congenital heart disease (References 31, 32). It has been reported that pharmacotherapy is often more effective in patients younger than 3 years compared with patients older than 3 years (Reference 21). Amiodarone has been used to treat FATs in infants and children, with high success rates of up to 100% (References 16, 33, 34). However, the adverse effect profile of amiodarone, compared with that of other agents, can be much higher (Reference 34). In a comparison study of infants treated with procainamide or amiodarone for supraventricular arrhythmias (excluding JET), continuous-infusion procainamide was shown to have a higher incidence of control without any greater incidence of adverse effects (Reference 35). Finally, sotalol has recently been used to treat patients with FATs with high rates of success (References 36–38). It appears that the best efficacy with sotalol occurs in younger patients who receive higher doses (Reference 30). The combination of flecainide and sotalol has been used to treat FATs and other arrhythmias with high success rates in patients who have been refractory to single-agent therapy (Reference 39).

Nevertheless, despite advances in antiarrhythmic therapy, β-blockers remain the most common first-line agent for the treatment of FATs.

Atrioventricular Nodal Reentrant Tachycardia

The first reentrant mechanism for supraventricular arrhythmias to be discussed is AVNRT. Of the two primary reentrant mechanisms, AVNRT is more common in older children, seldom occurring before 2 years of age (References 11, 40, 41). To have a reentrant rhythm, two separate pathways capable of conducting an action potential must be present. The pathophysiology of AVNRT consists of these two pathways within the AV node (termed *dual AV nodal physiology*), a slow pathway and a fast pathway, allowing a reentrant circuit (Reference 42) (Figure 2). In typical AVNRT, an ectopic beat must conduct down the slow pathway and then turn around and go back up the fast pathway to set up a circuit of rapid tachycardia (Reference 43). Most patients have the above typical AVNRT, with a few patients having atypical AVNRT consisting of conduction down the fast pathway and up the slow pathway (Reference 42, 44–47). Patients with AVNRT typically present with a rapid heart rate and, occasionally, chest pain, shortness of breath, and light-headedness. Those in prolonged tachycardia can present with signs and symptoms of heart failure. Neonates and infants will present with poor feeding, sweating while feeding, cough, cyanosis, and pallor with a marked decrease in activity (Reference 48). Typically, patients with AVNRT will present with a rapid heart rate and narrow QRS on ECG, with a P wave occurring immediately after the QRS (termed *short RP tachycardia*), but often, there are few differentiating characteristics from other supraventricular tachyarrhythmias (References 49, 50). Ablation of the slow pathway is often undertaken in the cardiac catheterization laboratory, with initial success rates greater than 95% in experienced centers and recurrence rates after ablation of less than 10% (References 45, 47, 51).

The goal of pharmacotherapy is to block the reentrant cycle within the AV node. Using antiarrhythmic medications to increase the refractory period, decrease automaticity, and/or decrease conduction velocity, the cycle can be broken. Initial management consists of vagal maneuvers and adenosine. The pharmacotherapy for AVNRT is highly varied, and many modalities have been used. Medications that decrease AV nodal conduction (digoxin, β-blockers, verapamil) are typically initiated as first-line oral agents and have a high rate of efficacy (References 46, 52). Propranolol is usually the first-line choice for a β-blocker in infants (Reference 53). Atenolol and nadolol have also been used in the treatment of AVNRT in older children (Reference 54). The percentage of breakthrough in patients receiving β-blockers is not insignificant, even if tachycardia is initially well controlled (Reference 41). Flecainide and propafenone have also been used for arrhythmias recalcitrant to initial therapies. Of the class Ic agents, flecainide has the largest experience in the treatment of refractory AVNRT, with up to 100% resolution of arrhythmias in one report and 81% success in another, but flecainide is contraindicated in the presence of congenital heart disease (References 31, 55). Few data exist for the use of amiodarone in AVNRT, potentially because of the high resolution rates with other antiarrhythmic

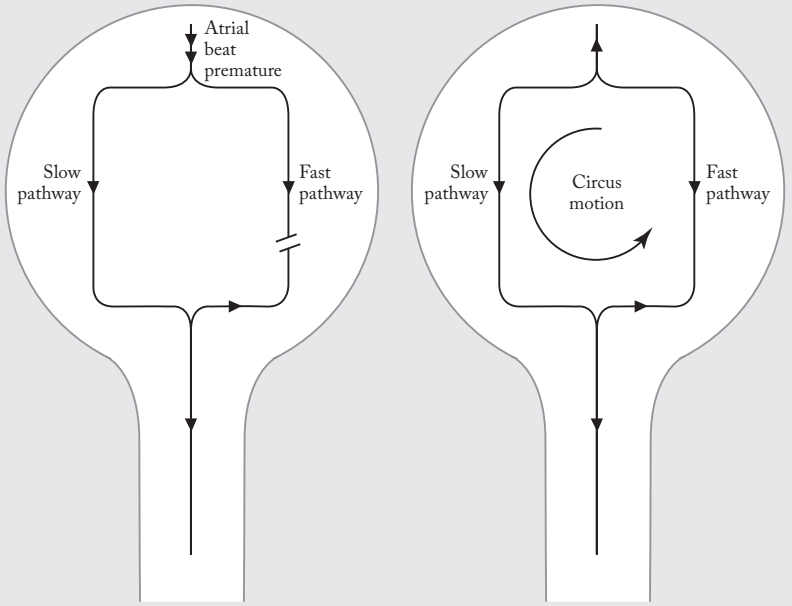


Figure 2. Atrioventricular nodal reentrant tachycardia.

This figure shows the dual pathways that can occur in an atrioventricular node. The fast pathway typically conducts before the slow pathway and is refractory when the slow pathway reaches it, thus causing the slow pathway conduction to stop. However, a premature atrial beat may cause extra conduction down the slow pathway, which then conducts retrograde up the fast pathway, resulting in a reentrant circuit (sometimes referred to as "circus motion"). This is termed atrioventricular nodal reentrant tachycardia (AVNRT).

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agents. Amiodarone appears to be a suitable last-line agent for arrhythmias refractory to all other agents on the basis of reports of effectiveness when treating other arrhythmias (References 56, 57). Similarly, sotalol has few data describing its use in AVNRT, although initial data are favorable as treatment of refractory AVNRT (References 58, 59).

In conclusion, the greatest body of evidence suggests that first-line therapy for AVNRT is a β-blocker or digoxin. In general, medical therapy is used in very young patients who may be at higher risk of complications during a catheter-based ablation procedure. Recalcitrant arrhythmias should be treated with flecainide, sotalol, or amiodarone.

Accessory Pathway–Mediated Reentrant Tachycardias

The second mechanism for reentrant arrhythmia uses an accessory pathway as an essential component of the tachycardia circuit. These are known as atrioventricular reentrant tachycardias (AVRTs) and are composed of two major subsets: WPW syndrome and concealed accessory pathways including permanent junctional reciprocating tachycardia (PJRT).

To have an accessory pathway–mediated tachycardia, four components are necessary: the atrium, the AV node, the ventricle, and the accessory pathway. Most commonly, an ectopic beat travels down the AV node and activates the ventricle, resulting in retrograde conduction up the accessory pathway to the atrium and back down the AV node (orthodromic tachycardia) (Figure 3). Although many accessory tracts have been identified, the most common is the Kent bundle, a residual fiber along the AV valve annulus, allowing electrical conduction between the atrium and the ventricle. Accessory pathway–mediated tachycardias can be distinguished by the direction of the impulse through the accessory tract during tachycardia: antidromic (from the atria to the ventricles) or orthodromic (from the ventricles to the atria) (Reference 60). Evidence of an accessory pathway can sometimes be seen on the surface ECG, with findings of a short PR interval, a slurred QRS upstroke (delta wave), and a wide QRS complex, and is considered the classic definition of the WPW pattern of ventricular preexcitation (Reference 60). Wolff-Parkinson-White syndrome is diagnosed by the presence of preexcitation on an ECG and evidence of a supraventricular tachycardia (SVT). Accessory pathways with only retrograde conduction cannot be seen on a surface ECG and are termed *concealed accessory pathways*, which can still create a circuit for AVRT (Reference 60).

Orthodromic tachycardia, the most common form of AVRT, usually appears as a narrow QRS tachycardia (which is often difficult to distinguish from AVNRT on ECG) (Reference 60). This is because the ventricles are depolarized by the normal conduction system, and the accessory tract is conducting retrograde in tachycardia. Antidromic AVRT occurs less often, is marked by ventricular preexcitation, and is more often a wide QRS complex because of more rapid ventricular activation through the accessory pathway (Reference 60).

Most patients with SVT presenting at younger than 1 year will have some form of accessory pathway–mediated tachycardia. More than 90% will spontaneously resolve by 1 year of age (Reference 7). However, a recurrence rate of about 30% has been reported after initial resolution (Reference 61). An increased incidence of

supraventricular arrhythmias occurs in infancy and then again later in childhood, with a final peak in adolescence (Reference 61). The long-term prognosis for patients with WPW is excellent for those with structurally normal hearts, in the absence of other comorbidities (References 9, 43). However, asymptomatic pediatric patients with WPW left untreated have about a 55% chance of becoming symptomatic by age 40 (Reference 62). Evaluation of all patients with WPW is necessary to prevent long-term morbidity, including risk of atrial fibrillation and risk of developing cardiomyopathy.

Initial treatment of AVRT is similar to treatment of other supraventricular arrhythmias (vagal maneuvers and adenosine). Long-term management of AVRT often includes ablation of the accessory tract, which has been shown to be very successful and is considered the standard of care by many (References 43, 63–68).

The goals of pharmacotherapy are to break the reentrant cycle by decreasing the automaticity of the pacemaker cells, decreasing the conduction velocity, and/or increasing the refractory period. As previously described, adenosine is often used as initial pharmacologic therapy before a definitive diagnosis.

Digoxin was a mainstay of treatment in patients with AVRT and WPW for decades, and some practitioners still use it (References 69–72). Digoxin can decrease the refractory period of the accessory pathway in WPW, and it can increase the signal transmission from the atria to the ventricles, potentially resulting in rapid ventricular conduction in patients with atrial fibrillation (Reference 73). However, some consider this primarily a risk to patients younger than 1 year because accessory pathway refractory periods are much shorter in children than in adults (Reference 71). Even though digoxin has been used effectively in pediatric patients with WPW and SVT, other agents have shown similar efficacy without the risk of ventricular arrhythmias (Reference 7).

As with digoxin, verapamil use has been discouraged in the treatment of AVRT because it also decreases the refractory period of accessory pathways and can result in rapidly conducted ventricular arrhythmias (References 7, 74–77). Verapamil, particularly the intravenous formulation, is contraindicated in neonates and infants because of the risk of cardiovascular collapse.

β-Blockers are most often considered the first-line agent for patients with AVRT (References 7, 58). Propranolol, atenolol, and nadolol have all been used with high efficacy and low adverse event profiles in pediatric patients (References 7, 53, 54, 78–80). In patients with a need for intravenous medication, such as postoperative patients, intravenous esmolol has been used to treat supraventricular arrhythmias (References 81–87).

Traditionally, the use of class Ia agents (quinidine or, more commonly, procainamide) is a next step in patients who are not controlled with β-blockade (References 7, 8, 41). The intravenous form has been used in infants and neonates, but with few data on efficacy for refractory AVRT (References 72, 89, 90).

A substantial body of literature is associated with the use of class Ic agents in patients with WPW. Propafenone was initially a drug of choice for patients whose previous therapies had failed (References 27–29, 91, 92). Now, oral flecainide represents an effective option for patients with supraventricular arrhythmias and WPW because of the large body of experience with the agent (References 31, 39, 55, 93–100). Clinicians, however, are hesitant to use flecainide in patients with structural heart disease (i.e., congenital heart disease) because of the increased mortality risk identified in adult and pediatric data (References 101–103).

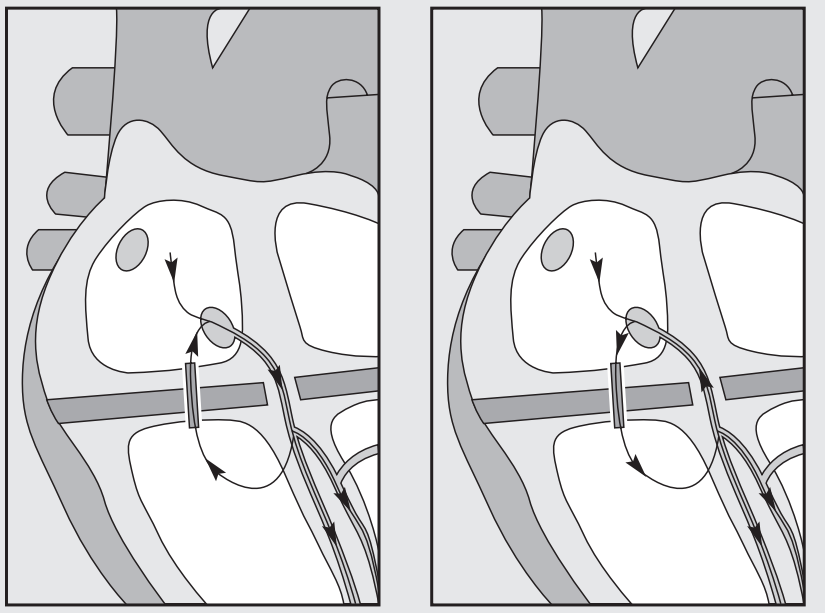


Figure 3. Accessory pathway reentrant arrhythmias.

This diagram represents orthodromic (left) and antidromic (right) reentrant tachycardia through a Kent bundle. The reentrant circuit is started when an ectopic beat conducts through the atrioventricular node.

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The class III agents are often reserved for the treatment of refractory AVRT, but they can be very effective. Amiodarone has been used with high rates of success (60% to 100% complete resolution), but it has also been reported to have a high incidence of adverse events, including hypotension, QT prolongation, and proarrhythmia (References 34, 88, 104–106). Sotalol has also been used for refractory WPW with good success, but the published experience to date has been much smaller than with other agents (References 37, 38, 59, 107–109). In addition, the risk of ventricular proarrhythmia, caused by QT-interval prolongation and development of torsades de pointes (TdP), and hypotension are concerns with sotalol.

In summary, oral β-blockers are the typical first-line agents for the treatment of supraventricular arrhythmias in patients with WPW. Patients with refractory arrhythmias may benefit from the addition of a second agent before progressing therapy to a class III agent. Depending on the patient's age, ability to take oral medications, and underlying pathophysiology, intravenous procainamide or oral flecainide is a reasonable next step. Finally, before multiagent therapy, oral or intravenous amiodarone or sotalol may be used.

Permanent Junctional Reciprocating Tachycardia

Although a large portion of supraventricular arrhythmias are caused by reentrant mechanisms, PJRT as a subset is relatively rare. Permanent junctional reciprocating tachycardia differs from the other reentrant tachycardias because it is characterized by an accessory pathway that exhibits only slow decremental retrograde conduction from the ventricles to the atria (Reference 60). This results in an ECG pattern of long RP tachycardia with inverted P waves in the inferior leads. Permanent junctional reciprocating tachycardia is often incessant and, if left untreated, can result in cardiomyopathy and heart failure (References 60, 110, 111). Although PJRT can spontaneously resolve, it has a high degree of morbidity caused by incessant tachycardia, which often forces practitioners to treat it (References 110–112). Depending on age, the refractory nature of the tachycardia, and ventricular function, use of ablation is often considered the standard of care for older children with PJRT (rarely in infants) (References 110, 111).

Pharmacotherapy for PJRT consists of case reports or case series because of the relative infrequency of the arrhythmia. Drugs used have included propranolol, flecainide, propafenone, sotalol, and amiodarone (References 27, 31, 59, 105, 112). β-Blockers alone are often ineffective. Propafenone has been used with limited success (References 26, 27). Early experience with treatment of PJRT showed success with flecainide, in which six of seven patients were successfully treated (Reference 31). Amiodarone was also used early with limited success (about 50% resolution) (Reference 105). Multidrug therapy has also been used to treat PJRT, using flecainide and propranolol, flecainide and sotalol, or amiodarone and propranolol (Reference 112). The largest study of PJRT reported that most patients (79%) did not respond to first-line therapy and that as many as nine different pharmacotherapeutic strategies had to be tried before control was gained. The highest rate of complete or partial effectiveness (84% to 94%) occurred with either amiodarone or verapamil (alone or in combination with digoxin) (Reference 110).

Permanent junctional reciprocating tachycardia is a difficult arrhythmia to treat with antiarrhythmic medications, and few data are available to guide therapy. β-Blockers remain first-line therapy. However, escalation of therapy to class I, class III, class IV, or multidrug regimens is likely.

Atrial Flutter, Atrial Fibrillation, and Intra-atrial Reentrant Tachycardia

The last three supraventricular arrhythmias are addressed together because of their shared characteristics and relative infrequency in the pediatric population. These arrhythmias are often considered "macro-reentrant" tachycardias because the entire atrium often consists of one large reentrant circuit (References 6, 113–116). Atrial flutter and atrial fibrillation are rare in neonates, infants, and children and are often found in patients with concomitant heart disease and in patients who have undergone surgical correction of congenital heart disease (References 6, 113–118). Presentation of atrial flutter in neonates typically occurs within the first 48 hours of life (Reference 116). Atrial flutter appears as a "saw-tooth" pattern on ECG, whereas atrial fibrillation is described as "irregularly irregular" (Reference 119). Intra-atrial reentrant tachycardia (IART) has also been termed *scar flutter* because it is seen in patients with a history of heart surgery. Direct current cardioversion is often used to convert patients to normal sinus rhythm (with anticoagulation possibly indicated before cardioversion) (References 6, 113–116). First-line therapy for IART is pharmacologic, but patients often require catheter ablation, placement of implantable pacemakers or cardioverters-defibrillators, or surgery (Reference 120). The use of transesophageal pacing for conversion of atrial flutter and atrial fibrillation in neonates and infants has shown success, but direct current cardioversion remains the mainstay of therapy (Reference 118). However, for older children, the presence of atrial fibrillation or IART, particularly in conjunction with congenital heart disease, is often treated with pharmacotherapy before cardioversion or in conjunction with cardioversion, depending on a patient's hemodynamic state (Reference 121).

Many agents have been used in the treatment of atrial flutter. Atrial flutter in neonates may not require pharmacotherapy, because rates of spontaneous conversion, or use of cardioversion, can resolve the arrhythmia with a low incidence of recurrence (References 113, 116, 122–124). Neonates with atrial flutter have historically been treated with digoxin, despite the low rates of success (less than 50%), and most clinicians would not treat a patient for longer than 1 year after diagnosis if there were no signs of recurrence (References 113, 116, 122, 124). β-Blockers, including propranolol, have often been used as a first-line agent for the treatment of neonatal atrial flutter after cardioversion (References 123, 125, 126). Other agents such as amiodarone, procainamide, quinidine, and sotalol have also been used for the treatment of neonatal atrial flutter (References 38, 113, 127–131). Treatment of atrial flutter in older infants and children has shown efficacy with the use of propafenone but poor results with the use of flecainide (References 27, 31, 32, 92). Amiodarone may be the most effective agent for the treatment of atrial flutter in infants and children, showing a 94% resolution rate (Reference 121). Sotalol has also been used, however, with lower rates of conversion than with amiodarone (References 108, 128). Overall treatment recommendations for neonates with atrial flutter include a β-blocker as a first-line therapy, but progression to other agents may be necessary for intractable arrhythmias. Infants and older children with atrial flutter may benefit from amiodarone, but the adverse events that can be associated with it must be weighed against the benefit gained.

Atrial fibrillation pharmacotherapy has primarily been extrapolated from adult data, because atrial fibrillation is extremely rare in children but common in adults. Digoxin has been used to slow ventricular response in atrial fibrillation with the addition of procainamide or quinidine if therapy initially fails (References 117, 132, 133). Often, progression of pharmacotherapy to sotalol or amiodarone becomes necessary (References 109, 128). Currently, the data for treatment of atrial fibrillation are sparse and likely subject to institutional bias; thus, treatment decisions should be considered on a case-by-case basis.

Junctional Ectopic Tachycardia

Although JET is a rare supraventricular arrhythmia, the mortality and morbidity associated with JET can be as high as 35% to 40% (References 6, 22, 134–145). Junctional ectopic tachycardia is most often associated with postoperative cardiac surgical patients and patients with myocarditis (pJET) (References 6, 22, 134–142). The ECG pattern of JET can have a wide or narrow QRS complex depending on the presence of underlying bundle branch block. It classically has a QRS morphology similar to that of sinus rhythm for that particular patient (Reference 22). Early recognition and treatment of JET is important because the tachycardia can result in profound decreases in cardiac output and lead to cardiovascular collapse, particularly in the postoperative patient (Reference 146). Patients with JET will often present in severe heart failure (Reference 147). Junctional ectopic tachycardia can be particularly difficult to treat because the tachycardia-associated decrease in cardiac output can result in increased adrenergic tone, which can subsequently further increase the junctional rate (Reference 22). Nonpharmacologic interventions for the treatment of pJET include cooling of the patient to reduce automaticity, sedation, decrease in environmental stimuli, reduction in inotropic agents, overdrive pacing, or His bundle ablation (References 22, 143–145, 148, 149). Congenital JET (cJET) typically is not as life threatening as pJET, but unlike pJET, which can resolve in 48–72 hours, cJET often requires chronic treatment (References 22, 135, 138, 142). In addition, 50% of patients with cJET have a family history of JET (Reference 22).

For pJET, intravenous amiodarone should be considered a first-line agent after nonpharmacologic intervention (References 34, 150–152). Other agents such as digoxin or propafenone have been previously used with much lower success rates (References 92, 153). Before cardiac surgery, the supplementation of magnesium and use of propranolol have both been shown to decrease the incidence of pJET (References 149, 154). The treatment of cJET with amiodarone has also shown good results, whereas the use of a β-blocker with or without digoxin has been fairly unsuccessful (Reference 142). Oral propafenone has shown variable results in treating cJET, yet it can still be considered an agent for initial therapy (References 28, 155, 156). Finally, sotalol has also been used for the treatment of cJET in some patients (References 107, 137). The most effective agent for the treatment of pJET or cJET at this time appears to be amiodarone.

Ventricular Tachyarrhythmias

Ventricular tachycardia (VT) and ventricular fibrillation (VF) are of great concern, particularly because of their association with sudden cardiac death in children and adolescents. This section will focus on VT and the subsequent potential progression to VF in pediatric patients.

VT and Fibrillation

The etiologies of VT in pediatric patients are varied, and they differ considerably from typical adult etiologies. Patients with congenital heart disease, particularly patients with tetralogy of Fallot, have been noted to have a higher incidence of VT than the general pediatric

population (Reference 157). In addition, patients with cardiomyopathies, such as hypertrophic cardiomyopathy or left ventricular noncompaction syndrome, are at a very high risk of sudden death because of VT leading to VF (Reference 158). Other etiologies of VT include surgery for congenital heart disease, genetic disorders (Brugada syndrome, long QT syndrome [LQTS]), catecholamine-sensitive polymorphic tachycardia, arrhythmogenic right ventricular dysplasia, myocarditis, and electrolyte disturbances (References 6, 159, 160). Many drugs have been implicated in the development of VT, primarily caused by QT-interval prolongation and TdP, which will be addressed in a separate section. Despite the many identified pathologies for VT, the etiology is often idiopathic. The incidence of spontaneous VT has been reported to be as high as 3% in patients with no preexisting cardiac disease (References 161, 162).

Pediatric patients with VT can present with chest pain, syncope with exertion, or cardiac arrest (Reference 163). Ventricular tachycardia is defined as three or more consecutive beats originating in the ventricles, and it appears as a wide QRS complex tachycardia on ECG (References 163, 164). Long-term prognosis of pediatric patients with VT is variable and dependent on many factors. These include the etiology of VT, severity of cardiovascular compromise with VT, and patient comorbidities (Reference 165).

Treatment of patients with VT requires that their hemodynamic status be considered before therapy initiation. Patients with hemodynamic compromise caused by VT/VF are emergently treated according to Pediatric Advanced Life Support (PALS) guidelines (Reference 166). For in-depth summaries of acute pharmacologic management of VT/VF, the PALS algorithms should be consulted (Reference 166).

Patients with chronic episodes of hemodynamically stable VT are managed differently, with the focus on prevention of VT/VF by medical or pharmacologic interventions. First-line therapy for chronic management of nonsustained VT in pediatric patients is often β-blockers, but this has been extrapolated from adult data (Reference 167). Atenolol, metoprolol, or nadolol have been used for treatment of VT and LQTS in children, whereas propranolol has been used in infants (References 168, 169). Mexiletine has also been used for the treatment of ventricular arrhythmias in pediatric patients with congenital heart disease (References 115, 170). Pharmacotherapy for the prevention of VT/VF often depends on the underlying substrate for VT; therefore, first-line therapies should be employed on the basis of patient-specific pathophysiology. Primary therapies that have been evaluated include β-blockers or amiodarone (Reference 165). Disopyramide can also be considered for patients with VT and hypertrophic obstructive cardiomyopathy as an adjunct to β-blockers (Reference 171).

Torsades de Pointes

Torsades de pointes is a form of polymorphic VT that is associated with a prolonged QT interval, which was previously discussed. Torsades de pointes occurs because of prolongation of the QT interval, which can occur with various disease states, including congenital LQTS, drug-induced long QT, and other forms of acquired long QT (Reference 172). Patients with a QT interval of 450 milliseconds or greater if they are males or 460 milliseconds for females on ECG are considered to have prolonged QT interval and therefore are at risk of TdP or other ventricular arrhythmias (References 172, 173). These numbers, however, are not absolute, and a patient's entire clinical scenario should be evaluated when determining QT-interval prolongation. Electrocardiographic findings for TdP are reflective of its name: the peaks of the QRS complexes appear to "twist"—thus, the name torsades de pointes, or "twisting of the points" (Reference 164). Many medications have been implicated in causing TdP, with prolongation of the QT interval as the most common reason for the removal of medications from the market in the United States (Reference 174). A table with selected medications that cause QT-interval prolongation and that may be used in pediatric patients has been provided (Table 2).

Management strategies are 2-fold: prevention of TdP and treatment of patients with TdP. Prevention of TdP focuses on the management of congenital LQTS, maintenance of electrolyte homeostasis, and minimization of exposure to medications that can potentially prolong the QT interval. It is beyond the scope of this chapter to summarize all the information associated with congenital LQTS because the various mutations often dictate pharmacotherapy (References 175, 176). In general, β-blocker therapy is indicated as first-line pharmacologic therapy in patients with high-risk LQTS mutations. If the mutations for LQTS affect sodium channels, mexiletine and flecainide have shown some initial benefit in adult patients (Reference 177). Patients may occasionally require a pacemaker or an implantable cardioverter defibrillator.

Acute management of TdP requires the use of intravenous magnesium sulfate for treatment (25–50 mg/kg/dose) and subsequent removal of any medications that may be prolonging the QT interval (References 178, 179).

Bradyarrhythmias

Two primary forms of bradyarrhythmias are most commonly seen in pediatric patients: sinus bradycardia and AV nodal block.

Table 2. Select Medications Responsible for QT Prolongation That May Be Used in Pediatric Patients[a]

Class	Medications
Class 1 (highest risk) These drugs will prolong the QT interval and may put patients at risk of proarrhythmia, including TdP.	Amiodarone Chlorpromazine Clarithromycin Disopyramide Erythromycin Haloperidol Methadone Pentamidine Procainamide Quinidine Sotalol
Class 2 (moderate risk) These drugs have some reports regarding QT-interval prolongation and may induce proarrhythmia in patients, but they do not currently have sufficient evidence for causing TdP. Patients may be at risk of TdP if these medications are used with other risk factors for the development of TdP.	Amantadine Azithromycin Chloral hydrate Dolasetron Escitalopram Flecainide Foscarnet Fosphenytoin Granisetron Levofloxacin Nicardipine Octreotide Ondansetron Quetiapine Risperidone Tacrolimus Venlafaxine Voriconazole
Class 3 (low risk) Drugs that have weak evidence for the development of TdP and that would be unlikely to cause arrhythmia when used in normal doses in patients without other risk factors	Amitriptyline Ciprofloxacin Citalopram Diphenhydramine Fluconazole Fluoxetine Imipramine Itraconazole Paroxetine Ritonavir Sertraline Trazodone Trimethoprim/sulfamethoxazole

[a]Medications and classifications are constantly modified according to the most recent literature. For complete listings and classifications of medications, see www.qtdrugs.org.
TdP = torsades de pointes.
Adapted from Reference 218.

Sinus Bradycardia

Sinus bradycardia is defined as a heart rate less than the lower limit of normal values, and it can occur in a wide variety of patient subsets, from preterm infants to well-trained athletes (References 180–187). Rarely is sinus bradycardia a cause for medical treatment unless hemodynamic instability occurs, such as in cardiogenic shock or if the patient has notable symptoms related to bradycardia. Patient presentation for bradycardia can vary on the basis of age and can include poor feeding and lack of weight gain (in neonates and infants), fatigue, exercise intolerance, and, in severe bradycardia, cardiogenic shock or seizures (Reference 185). Sinus node dysfunction, or "sick sinus syndrome," is a common cause of sinus bradycardia. Etiologies of sinus node dysfunction include medications, excessive vagal tone, electrolyte imbalances, elevated intracranial pressure, and congenital heart disease (particularly after repair of a congenital heart lesion) (Reference 183). A genetic component to sinus node dysfunction has been identified that is associated with LQTSs (References 188, 189). Cardiac pacing is an option because pharmacotherapy for sinus bradycardia is not currently indicated. Limitation or removal of agents that can cause sinus bradycardia, or correction of preexisting patient pathophysiologies that can lead to bradycardia, is warranted (Reference 183).

AV Nodal Block

Atrioventricular nodal block, defined as a delay in signal conduction from the atria to the ventricles, primarily involves the AV node and/or the bundles of His (Reference 183). Atrioventricular block is classified according to the degree of PR-interval prolongation and the association of P waves with QRS complexes. First-degree AV block, or PR-interval prolongation in adults, is defined as a PR interval greater than 0.2 millisecond while maintaining a 1:1 atria-to-ventricle conduction ratio. Second- and third-degree (or complete) AV block are characterized by increasing the degree of AV dissociation (Reference 183). Complete AV block has no associated conduction between atria and ventricles, and it is characterized by an atrial rate that is higher than the ventricular rate (Reference 183).

Primary modalities for treatment of higher-grade or symptomatic AV block include pacemaker insertion and correction of the underlying pathophysiology that is leading to AV block (Reference 190). Removal of offending agents, such as medications, is indicated for the treatment of AV block. Pharmacotherapy is rarely beneficial as primary treatment.

Antiarrhythmic Agent Selection

As shown throughout this chapter, many different agents can be used to treat similar arrhythmias, and single agents can be used in a wide variety of indications.

The basic pharmacology of each class will be reviewed, and salient points will be addressed regarding each of the antiarrhythmic agents discussed in the chapter that may affect decision-making when initiating pharmacotherapy. Specifically, this section will focus on dosing, drug concentration monitoring, dosage forms, and adverse events. Dosing information has been summarized (Table 1). For other information regarding antiarrhythmic drug properties, such as pharmacokinetic parameters, the reader is urged to consult a comprehensive drug reference (Reference 5).

Class Ia

The class Ia agents block sodium channel uptake in the fast sodium channels. In relation to other class I agents, the blockade would be considered moderate, and the resultant effects of decrease in automaticity, increase in refractory period, and decrease in conduction velocity would also be considered moderate. The QT interval can be moderately prolonged, with little to no effect on QRS duration or PR interval. Left ventricular dysfunction and hypotension with therapy have been noted (References 30, 58).

Quinidine

Quinidine has been used to treat children with rare arrhythmias, such as the Brugada syndrome (Reference 191). Pharmacokinetic studies highlighting doses with quinidine have been performed (Reference 192). Clearance of quinidine is inversely proportional with age in pediatric patients; therefore, younger patients may require higher doses (Reference 193). A trough serum concentration of 2–7 mcg/mL is considered therapeutic for the treatment of arrhythmias (Reference 5).

However, quinidine is not used often because of the high rate of adverse events, proarrhythmia (TdP), central nervous system toxicity, and hypotension with the intravenous form (Reference 194). Quinidine is available in two different forms (gluconate and sulfate), with dosing differences between them, and requires special attention to minimize medication errors. Careful consideration should occur before the use of quinidine regarding the risk-benefit ratio. There is a formulation for an extemporaneous preparation of a suspension (Reference 195).

Procainamide

There is a paucity of data for the dosing of procainamide in neonates, infants, and children. The dosing and monitoring strategies have been primarily extrapolated from adult literature. Intravenous dosing consists of a loading dose followed by a continuous infusion of 20–80 mcg/kg/minute, with doses to achieve therapeutic concentrations on the lower end for neonates and preterm neonates, likely because of decreased clearance (References 90, 196). Patients with renal dysfunction or receiving renal replacement therapy have reduced clearance of procainamide and metabolites and require dosage adjustments (Reference 90).

Drug level monitoring is indicated for intravenous procainamide. Concentrations of procainamide and its active metabolite, *N*-acetyl procainamide (NAPA), are drawn after an intravenous bolus and every 12 hours during continuous-infusion therapy (Reference 5). Goal concentrations have been reported at 4–10 mcg/mL for procainamide, but they can vary depending on institutional practices (Reference 5). Procainamide therapy is usually not titrated to NAPA concentrations, but these concentrations are useful to determine whether the patient is a "fast acetylator" (a NAPA/procainamide ratio of 1:1 or greater) and will therefore need higher doses (Reference 90).

The most common adverse events associated with procainamide are hypotension, primarily with continuous-infusion administration, and proarrhythmia, such as heart block. Recent reports have documented that procainamide is associated with fewer adverse events than amiodarone, with similar efficacy in certain situations (Reference 35).

Disopyramide

Minimal data are available for disopyramide use in pediatric patients because newer agents have been shown to be more effective at controlling arrhythmias or have fewer adverse events (Reference 171). Disopyramide dosing should be adjusted in patients with renal dysfunction (Reference 5). Serum concentrations of disopyramide can be measured, though there is no correlation with drug efficacy in pediatric patients (Reference 5). Adverse events with therapy include proarrhythmia (Reference 5). There is a formulation for an extemporaneous preparation of a suspension (Reference 5).

Class Ib

Medications in class Ib are considered to have the least potent sodium channel blockade, affecting the fast sodium channels in the phase 0 upstroke of the action potential. Class Ib agents decrease both automaticity and conduction velocity and increase the refractory period, but all effects are to a lesser extent compared with the other class I antiarrhythmics. There is little effect on the QRS duration, PR interval, QT interval, or left ventricular function.

Lidocaine

Lidocaine can be given as an intravenous bolus or as continuous infusion for acute ventricular arrhythmias (Reference 5). Pharmacokinetic parameters have been described in pediatric patients with congenital heart

disease (Reference 197). Serum lidocaine concentrations can be monitored at steady state to prevent toxicity, with goal ranges reported from 1.5 to 5 mcg/mL (Reference 5). Hypotension, central nervous system toxicity, and proarrhythmia have been noted as adverse events upon bolus intravenous injection or continuous intravenous infusion (Reference 5).

Mexiletine

A paucity of data exists for the use of mexiletine in pediatric patients for treating ventricular arrhythmias and certain types of LQTS (References 170, 198). Mexiletine is structurally similar to lidocaine, but orally active. Serum mexiletine concentrations can be monitored as trough concentrations to minimize toxicity (Reference 5). Potential adverse events include proarrhythmia and ataxia (Reference 5). There is a formulation for an extemporaneous preparation of a suspension (Reference 199).

Class Ic

The phase 0 upstroke involving sodium ion channel blockade is blocked to the greatest degree by class Ic agents. Similarly, decreases in automaticity and conduction velocity and increases in refractory period are the most pronounced of all the class I agents. The PR interval, QT interval, and QRS duration are all prolonged.

Flecainide

Dosing is controversial regarding whether dosing per kilogram or by body surface area should be used to achieve therapeutic concentrations (References 5, 31, 55). Flecainide interacts with milk; therefore, concentrations can be lower (or doses will need to be higher) in patients who are breastfeeding or receiving milk and concentrations may change when the patient's diet changes if not immediately given around a feed (References 5, 55). Sex, race, and cytochrome (CYP) P450 2D6 enzyme expression have been shown to affect flecainide disposition (References 200, 201). Flecainide is contraindicated in patients with congenital heart disease because of reports of increased mortality (Reference 101).

Flecainide concentrations can be monitored when initiating therapy and on a regular basis thereafter. Therapeutic range for treatment of arrhythmia is 0.2–1 mcg/mL drawn as a trough, but the utility of flecainide concentration monitoring on patient outcomes is unknown (Reference 5). Concentrations may not need to be measured if using low doses because the effectiveness of therapy can be monitored by QRS widening. In-hospital initiation of flecainide is usually required.

Adverse events are relatively uncommon, primarily consisting of neurologic changes and proarrhythmia (less than 1%), and they are rare when concentrations are within therapeutic ranges (References 5, 55). There is a formulation for an extemporaneous preparation of a flecainide suspension (Reference 5).

Propafenone

Propafenone dosing is controversial regarding whether milligram-per-kilogram dosing or body surface area should be used (References 5, 27, 91). Patients who received the lower range of dosing had decreased effectiveness when undergoing treatment of WPW compared with patients who received higher doses (300–380 mg/m^2/day) (Reference 58). Level monitoring is not typically used for propafenone because levels do not correlate well with ECG parameters (Reference 202). There is a formulation for an extemporaneous preparation of a suspension (Reference 203).

Class II

The β-blockers make up the class II agents and exhibit their actions primarily on the pacemaker cell action potentials by limiting catecholamine stimulation. These effects primarily result in decreased automaticity, and they subsequently increase the effective refractory period of the Purkinje fibers. Use of β-blockers can acutely decrease left ventricular function and will prolong the PR interval. There is usually no effect on the QT interval or QRS duration.

Propranolol

Standard dosing regimens for propranolol have been established, and most centers commonly use a maximum of 4 mg/kg/day (References 5, 8). Drug level monitoring for propranolol is not currently indicated.

Reported adverse events with propranolol include hypotension, bradycardia, and hypoglycemia. Caution should be used when a β-blocker is administered in a patient with reactive airway disease (Reference 5). Propranolol is currently available in two different concentrations of a commercially available solution: 4 mg/mL and 8 mg/mL for enteral use (Reference 5). Intravenous propranolol is also available, but with limited experience (Reference 5).

Esmolol

Esmolol can be used as a continuous infusion for treatment of supraventricular arrhythmias or ventricular arrhythmias (Reference 5). Pharmacokinetic and dosing studies have been performed in children, and esmolol is often used when a quick onset and short

half-life of β-receptor blockade are beneficial (References 81, 204). Adverse events are similar to those of other β-blockers and consist of bradycardia and hypotension (Reference 5).

Atenolol

Atenolol has been used for arrhythmias in children, but with less experience than other β-blockers such as propranolol (References 54, 168). Pharmacokinetic and pharmacodynamic studies have been performed with atenolol in children, and drug level monitoring is not currently indicated (References 54, 80, 205). Common adverse events associated with atenolol include bradycardia and hypotension (Reference 5). There is a formulation for an extemporaneous preparation of an atenolol suspension (Reference 5).

Metoprolol

Metoprolol has not typically been used for the treatment or prevention of arrhythmias in pediatric patients; thus, there are few data to guide therapy (References 169, 206). Metoprolol is more cardio-specific in its β-blockade than other β-blockers and may have a lower incidence of bronchospasm (Reference 5). Care should be taken that patients receive the correct formulation of tablet: metoprolol tartrate or metoprolol succinate (extended release). There is a formulation for an extemporaneous preparation of a suspension (Reference 207).

Nadolol

Pharmacokinetic studies have been performed for nadolol in children, and the authors of the study warn of using nadolol in children younger than 2 years because of wide variations in pharmacokinetic parameters (Reference 208). Common adverse events for nadolol include bradycardia and hypotension (Reference 5). No formulation for a suspension is currently available.

Class III

The class III agents exhibit their antiarrhythmic effects primarily through potassium channel blockade, extending phase 4 of the action potential and increasing the refractory period. However, agents in this class often have several mechanisms of action. Sotalol has nonselective β-blockade effects in addition to potassium channel blocking effects. Amiodarone has sodium channel blocking effects, β-blocking effects, and calcium channel blocking effects. Electrocardiographic findings in patients receiving class III antiarrhythmics include prolonged PR and QT intervals and increased QRS duration. The prolongation of the QT intervals places patients at risk of TdP. Hypotension can occur, particularly with intravenous amiodarone.

Sotalol

Sotalol dosing for neonates, infants, and children has been controversial. Currently, three dosing methods have been suggested for patients younger than 2 years (Reference 5). A dosing nomogram for patients younger than 2 years has been proposed, with reductions in dose for younger patients on the basis of body surface area (Reference 5). Other pharmacokinetic studies have been performed showing that lower doses of sotalol are effective in patients younger than 2 years but that sotalol should be dosed on a milligram-per-kilogram basis (References 209, 210). Recent data have supported dosing on body surface area, with no reduction in dose for age or renal function, with good outcomes (Reference 211). Younger patients may be more tolerant of higher doses of sotalol than older patients (Reference 30). The ideal method for dosing sotalol in this age subset is unclear. Monitoring of ECG for QT-interval prolongation is necessary when initiating or titrating therapy.

Primary adverse events associated with sotalol are arrhythmia related. Bradycardia and TdP can occur with sotalol use, and females are more likely to have TdP with sotalol compared with males (References 5, 194). Maintenance of electrolyte homeostasis (i.e., potassium) is important for preventing TdP, and frequent ECG monitoring is indicated. In-hospital initiation of sotalol is usually required.

Sotalol is available as a tablet, and there is a formulation for an extemporaneous preparation of a suspension (Reference 5). Intravenous sotalol has recently become available, though there is no pediatric experience to date with intravenous sotalol.

Amiodarone

Amiodarone can be dosed either on body surface area or per body weight for continuous-infusion or chronic therapy (Reference 5). In the acute setting, body weight dosing is primarily used for intravenous bolus (Reference 5). Amiodarone serum concentrations can be drawn, but few data are available to interpret concentrations or their effect on antiarrhythmic efficacy (References 212, 213).

Many adverse events are associated with amiodarone therapy. Pulmonary fibrosis, thyroid toxicity, corneal deposits, hepatotoxicity, decreased growth, developmental delay, dermatologic hypersensitivity, and proarrhythmia (i.e., TdP) have all been reported with amiodarone therapy, and a baseline evaluation for potentially affected organ system function is warranted (References 214–217). Hypotension is a common adverse event after the intravenous administration of amiodarone (References 218, 219). Some centers may precede an infusion of amiodarone with an infusion of calcium to prevent hypotension. Drug interactions with amiodarone are also significant because it affects CYP enzymes and P-glycoprotein drug transport mechanisms (Reference 5).

Although an intravenous formulation of amiodarone is available, it is only compatible with a 5% dextrose solution (Reference 5). In addition, amiodarone intravenous solutions must be given through tubing that does not have bis(2-ethylhexyl)phthalate (DEHP) in the formulation because a solubility component of intravenous amiodarone (Tween 80) has been noted to leach DEHP from the tubing, potentially causing sterility in male patients (Reference 5). There is a formulation for an extemporaneous preparation of a suspension (Reference 220). Because amiodarone is highly lipid soluble, special care must be taken when preparing a suspension.

Class IV

The class IV agents include the nondihydropyridine calcium channel blockers. As opposed to dihydropyridine calcium channel blockers (i.e., nifedipine), the class IV agents more specifically act on the myocardium, and pacemaker cell action potential, by blocking slow L-type calcium channels. Calcium channel blockade decreases phase 4 depolarization by increasing the refractory period of the pacemaker cell and decreasing conduction velocity in the AV node. Electrocardiographic findings include an increased PR interval. These agents can decrease left ventricular function and cause hypotension; they are not recommended for children younger than 1 year.

Verapamil

Dosing for treatment or prevention of arrhythmias is not well established in pediatric patients, with limited pharmacokinetic studies performed to date (References 221, 222). In general, the use of verapamil in patients younger than 1 year is discouraged, despite some reports of successful use (References 223–225). Intravenous verapamil therapy for the treatment of arrhythmias in neonates and infants is discouraged because of instances of proarrhythmia, including AV block and cardiovascular collapse after administration (References 74, 77, 226). Different strategies to avoid the cardiovascular adverse effects have been tried, including administering intravenous calcium with verapamil and using slow infusion rates (Reference 227).

Verapamil is available in different extended-release formulations. Therefore, attention to dosage forms is important to minimize errors. There is a formulation for an extemporaneous preparation of a suspension (Reference 207).

Diltiazem

Few data are available for the use of diltiazem to treat or prevent arrhythmias in pediatric patients (Reference 228). Proarrhythmic effects, including AV block and hypotension, are two primary concerns for adverse events (Reference 5). Diltiazem is available as immediate- and extended-release formulations, and there is a formulation for an extemporaneous preparation of a suspension (Reference 229).

Digoxin

Digoxin acts by blocking the sodium/potassium ATPase pump in the myocardium, which results in decreased conduction velocity (by decreasing the rate of transmission through the AV node) and increased refractory period. Sinus bradycardia and AV block can occur, particularly when serum digoxin concentrations are elevated.

Digoxin use in pediatric patients for the treatment of arrhythmias has a large body of literature because it has historically been first-line therapy for many types of arrhythmias (References 30, 58). Pharmacokinetic studies of children have been performed to delineate dosing (Reference 230). Digoxin toxicity can occur in patients with renal dysfunction, electrolyte imbalances, or drug interactions (Reference 231). Serum digoxin concentrations are not indicated for routine therapy because concentrations do not correlate with efficacy, but they may be useful in the assessment of digoxin toxicity (Reference 232). In addition, neonates may have false-positive results for elevated digoxin concentrations because of digoxin-like interacting substances in the blood (Reference 233). Digoxin toxicity manifests as bradycardia (including AV block), nausea and vomiting, and visual disturbances (Reference 231). Digoxin-immune Fab is used to treat symptomatic digoxin toxicity (Reference 231). Digoxin should be avoided in patients with WPW.

Precautions should be taken when administering digoxin because dosing is in micrograms, and errors have occurred when using a commercially available digoxin solution (Reference 234).

Adenosine

Adenosine is an endogenous nucleoside that directly affects potassium currents, which depresses AV nodal function. The ECG often shows no conduction after the administration of adenosine (in reentrant arrhythmias), or depressed nodal activity, which lasts a few seconds.

Published experience with adenosine in pediatric patients is extensive (References 14, 235–240). Patients may require several doses of adenosine to achieve the desired effect. Adenosine, which has a short half-life (6–10 seconds), should be administered as a rapid intravenous push, followed by a rapid flush, through intravenous access that is closest to the heart, to ensure adequate delivery of the drug to the myocardium before metabolism (Reference 5).

Despite extensive experience with adenosine, adverse effects have been noted, including the generation of wide complex tachyarrhythmias (References 15, 241). Caution should be exercised when using

adenosine in patients with asthma because bronchospasm can occur. Only experienced personnel should administer adenosine in a setting where life-support equipment is available.

Conclusions

The pharmacotherapy for pediatric arrhythmias can be complex and highly variable. A comprehensive knowledge of arrhythmia pathophysiology and antiarrhythmic pharmacology and the impact of pediatric growth and development is essential to ensure optimal outcomes. Future efforts to refine the pharmacotherapy for pediatric arrhythmias are warranted to minimize morbidity and maximize efficacy.

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CHAPTER 11

Pediatric Hypertension

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Learning Objectives

1. Outline the history, incidence, and epidemiology of pediatric hypertension.
2. Review the pathophysiology, including neurohormonal and humoral pathways, of pediatric hypertension.
3. Describe the clinical presentation, criteria for diagnosis, blood pressure measurement methodology, and approach to management of pediatric hypertension and hypertensive emergencies.
4. Explain the pharmacology and pediatric implications for each drug class used in the treatment of pediatric hypertension and hypertensive emergencies.

Abbreviations in This Chapter

ABPM	Ambulatory blood pressure measurement
ACE	Angiotensin-converting enzyme
AHA	American Heart Association
ARB	Angiotensin receptor blocker
AT	Angiotensin
BP	Blood pressure
CCB	Calcium channel blocker
DBP	Diastolic blood pressure
ESH	European Society of Hypertension
4th Report	The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents
JNC VII	The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure
RAAS	Renin-angiotensin-aldosterone system
SBP	Systolic blood pressure
SVR	Systemic vascular resistance

Introduction

Ancient works have referred to hypertension as "hard pulse disease," but modern medicine most simply defines it as the persistence of elevated arterial blood pressure (BP) (Reference 1). Although the incidence of pediatric hypertension is relatively low, its damaging effects may be experienced throughout all age groups. Hypertension has been linked to increased morbidity and mortality in pediatric patients since the 1960s (References 2, 3). Yet not until the late 1960s were reference BP ranges for children developed. In the past 40 years, much research has focused on the identification, definition, and treatment of hypertension in the pediatric patient (Reference 4).

Research leading to a subsequent increase in pediatric hypertension literature has afforded clinicians more evidence-based resources to manage this disease state (Reference 4). In contrast to the available adult literature, the amount of quality pediatric data is limited. Also unlike existing adult data, robust clinical trials evaluating the treatment of pediatric hypertension are scant. Many studies suggest that pediatric hypertension "tracks" into adulthood; however, data showing that the treatment of pediatric hypertension reduces or prevents this tracking phenomenon are nonexistent (References 5–9). The most recent evidence-based efforts to aid pediatric clinicians in the management of hypertension were produced by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents in the United States in 2004 and the European Society of Hypertension (ESH) in 2009 (References 10, 11). This chapter will review pertinent aspects of these guidelines, including pathologic mechanisms, pharmacotherapy, and relevant recently published clinical literature regarding the treatment of pediatric hypertension and hypertensive emergencies.

History

Although the adverse effects of hypertension have been known in adult arenas since 2600 BC, pediatric medicine was late to recognize or even consider childhood hypertension without suggestive signs and symptoms until the late 1960s (References 1, 12). Established pediatric BP norms were unavailable in this era because normal values for pediatric hypertension were typically borrowed from adult literature. With the simultaneous contributions of the investigators of the Muscatine

and Bogalusa Heart Studies, which began in 1971 and 1972, respectively, interest and research in pediatric hypertension and cardiovascular disease began to gain momentum (References 13, 14). These studies helped pave the way for hypertension research in children and established the importance of evaluating pediatric BP on the basis of age, sex, and height.

Epidemiology

The incidence of hypertension in children and adolescents is about 1%–5% of the normal pediatric population (Reference 15). This is relatively low compared with a 28% incidence of hypertension in adults reported in 2006 (Reference 16). With evidence suggesting that youths with high BP are more likely to be hypertensive adults, diagnostic screening, preventive measures, and pharmacologic treatment of hypertension in children with the goal of minimizing potential long-term deleterious effects have been deemed of great importance by many expert clinicians (References 5–10).

Pathophysiology of Pediatric Hypertension

Cardiovascular function is regulated by a complex cascade of neurohormonal mechanisms that influence hemodynamics. Neural mechanisms include sympathetic tone, the baroreflex system, and cardiopulmonary reflex. Humoral regulation occurs through the renin-angiotensin-aldosterone system (RAAS), endothelial vasoactive factors, glucocorticoids, arginine vasopressin, and natriuretic peptides (References 17–21). Although many pathways exist, not one has proved to be the sole cause of essential pediatric hypertension. For this reason, many pharmacologic agents have been developed to address potential underlying imbalances in hemodynamic regulation mechanisms.

Neural Regulation

The central nervous system (CNS) plays an essential role in the regulation of BP by allocating autonomic tone to various areas of the cardiovascular system through receptors that detect pressure changes in the vasculature and changes in the chemical composition of the blood. These α- and β-receptors reside on the pre- and postsynaptic surfaces of sympathetic terminals and regulate norepinephrine release (References 18, 19, 22). Stimulation of central α_2-receptors inhibits the release of norepinephrine, whereas activation of central β-receptors has the opposite effect (References 18, 19, 22). The response seen on arterioles and venules because of peripheral α_1-receptor activation is vasoconstriction (References 18, 19). β_1-Receptors are very densely dispersed within the heart, and β_2-receptors are present in abundance within the lungs as well as the arterioles and venules. β_1- Activation produces an increase in heart rate and contractility, and β_2-activation causes vasodilation (References 18, 19).

The negative feedback mechanism regulating sympathetic tone and ultimately short-term BP control is called the baroreflex system (Reference 19). Receptors designed to detect changes in arterial BP are mainly located in the aorta and carotid arteries (References 18, 19). Other baroreceptors are located in the afferent arterioles of the kidneys, but their main role is involved in renin release (Reference 20). Increased baroreceptor activity occurs because of an acute intravascular pressure elevation that results in decreased heart rate and contractility in addition to peripheral vasodilation (References 18, 19). This effect is illustrated by the use of carotid massage to treat supraventricular tachycardia. By manually palpating the carotid artery, this nonpharmacologic intervention attempts to increase vagal tone by mimicking increased arterial pressure. An acute BP decrease has the opposite baroreceptor effect, causing vasoconstriction and an increase in heart rate and contractile force because of decreased baroreceptor activity. As children age, their physiologic normal BP increases with increasing body size (Reference 17). Baroreceptors subsequently adjust to changing BP norms as children age to help maintain safe hemodynamic control (Reference 17).

Humoral Regulation

Together with neural regulation, many humoral mechanisms contribute to the maintenance of cardiovascular function and homeostasis. Alterations in any or all of these mechanisms may lead to the pathologic development of hemodynamic abnormalities.

The RAAS is primarily regulated by the kidney's effect on electrolyte and fluid balance, sympathetic tone, vascular smooth muscle tone, and BP. In humans, angiotensin-converting enzyme (ACE) activity leads to increased production of angiotensin (AT) II, decreased bradykinin concentrations, sympathetic norepinephrine release, and aldosterone release. Inhibition of this pathway by ACE inhibitors such as captopril causes vasodilation, decreased afterload, increased cardiac output, and mild diuresis (References 20, 21, 23). In the first months of life, it is crucial to consider the differences existing in the RAAS. Plasma renin activity and subsequent AT II concentrations in newborns and infants are very high (Reference 23). This difference may cause significant hypotension in neonates if caution is not observed in dose initiation and titration of ACE inhibitors.

Other pharmacologic RAAS targets for antihypertensive effects in pediatric patients include AT-receptors (Reference 24). The pediatric AT_1-receptor regulates the function of the cardiovascular system, but the AT_2-receptor has no important role in cardiovascular homeostasis (Reference 24). Because the activation of AT_1-receptors produces direct arterial vasoconstriction, increased sympathetic tone, and aldosterone release, angiotensin receptor blockers (ARBs) are also used in children to combat hypertension.

Assessment of Pediatric BP

Together with a thorough knowledge of the physiologic mechanisms behind hemodynamic homeostasis in children, it is important to understand how to assess BP in pediatric patients. In this section, the differences between primary and secondary hypertension will be reviewed, together with appropriate pediatric BP measurement techniques, diagnostic criteria for pediatric hypertension, and normal physiologic BP ranges in infants, children, and adolescents.

BP Measurement

The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (4th Report) has recommended a methodology for measuring BP in children, which is listed in Box 1 (Reference 10). The 4th Report urges clinicians to begin routine BP measurements at 3 years of age because of the difficulty measuring BP in younger children. Neonates, infants, and toddlers can certainly develop hypertension, so care should be taken to routinely evaluate BP in children younger than 3 years if they have certain comorbid diseases as defined in the 4th Report (Reference 10). Examples include neonatal complications requiring intensive care, congenital heart disease, and kidney disease (Reference 10). For all patients, special consideration should be focused on investigating the presence of preexisting circumstances that may cause BP elevation at measurement. For example, an infant who is crying during measurement may have a falsely elevated BP compared with BP at rest. To aid the clinician in recognizing the pharmacologic causes of hypertension, a brief list highlighting common childhood and adolescent prescriptions, over-the-counter drugs, food, and supplements that can elevate BP are listed in Table 1 (References 25–27).

Blood pressure in pediatric patients should be measured by placing the stethoscope over the brachial artery (proximal and medial to the antecubital fossa) and just below the bottom edge of the BP cuff (References 28, 29). For pediatric patients, special attention should be placed on selecting the appropriate cuff size (References 28, 29). The American Heart Association (AHA) recommends selecting a cuff with a bladder that will cover 80% to 100% of the patient's arm circumference (References 28, 29). Children with large arms are recommended to use small, standard, or large adult cuffs and, if necessary, a thigh cuff (Reference 29). The importance of using the appropriate-sized cuff when measuring pediatric BP is paramount because using an incorrect size may provide false readings (Reference 29). Smaller cuffs tend to yield falsely high measurements, whereas larger cuffs underestimate BP (References 30, 31). It is recommended that infants and neonates (or patients with faint Korotkoff sounds) have an indirect BP measurement with an ultrasonic flow detector (Reference 32).

Diagnosis of Pediatric Hypertension

The 4th Report defines normal and abnormal pediatric BP values in percentiles with reference to age, sex, and height (Reference 10). The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VII) does not refer to specific patient characteristics,

Box 1. Methodology for pediatric BP measurement.

- Measure BP in patients > 3 years at each health care visit, < 3 years if certain conditions met.
- Auscultation preferred (normal BP values based on auscultation)
- Choose appropriate cuff size.
- Avoid stimulants (drugs or food) before measurement.
- Rest quietly for at least 5 minutes before measurement.
- Use right arm, seated position, back supported, feet resting on floor (supine position for infants).
- High blood pressure must be remeasured and confirmed on repeat visits to diagnose hypertension.
- BP > 90th percentile as measured by oscillometric technique must be confirmed by auscultation method.

Information from References 10 and 11.
BP = blood pressure.

Table 1. Substance-Induced Hypertension

Prescription Drugs	Drugs of Abuse	Food	Environmental Exposure	Drug Withdrawal
Amphetamines	Alcohol	Black licorice	Cadmium	Benzodiazepines
Cyclosporine	Anabolic steroids	Calcium	Lead	β-Blockers
Darbepoetin alfa	Caffeine	Sodium	Mercury	Clonidine
Epoetin alfa	Cocaine			Opioids
Ergot alkaloids	Ecstasy			
Glucocorticoids	Ephedrine			
Ketamine	Nicotine			
Levothyroxine				
Lithium				
Metoclopramide				
Nonsteroidal anti-inflammatory agents				
Oral contraceptive agents				
Phenylephrine				
Pseudoephedrine				
Scopolamine				
Tacrolimus				

Information from References 25–27.

but simply defines hypertension in adults as 140/90 mm Hg or greater (Reference 33). The JNC VII adult definitions of hypertension are based on known risk factors for cardiovascular disease (Reference 33). The strategy of using static systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements, as with adults, is inappropriate in children for two reasons. First, pediatric evidence linking hypertension to increased risk of cardiovascular disease is lacking. Second, because normal BP values change as children grow, clinicians must rely on data that compare pediatric BP values with those of their pediatric peers (References 10, 34). Population-based normal BP values (represented in percentiles) for children 1 year of age or older, grouped by age, sex, and height, have been published previously in the 4th Report and by the ESH (References 10, 11). These guidelines should be reviewed by any clinician involved in the diagnosis, evaluation, and treatment of childhood hypertension (References 10, 11). The ESH embraces the same principles regarding BP norms based on patient demographics, but of note, the normal values listed by the 4th Report are slightly lower than the European values across each demographic category (References 10, 11). Thus, it is recommended that U.S. clinicians follow the 4th Report BP values when diagnosing and treating hypertension, whereas Europeans should follow the ESH report. Guidelines for normal BP values in newborns and infants can be found in the Report of the Second Task Force on Blood Pressure Control in Children (Reference 34). Definitions of varying severities of hypertension in children and adolescents based on percentiles for age, sex, and height are listed in Table 2 (Reference 10).

Ambulatory Blood Pressure Measurement

Ambulatory blood pressure measurement (ABPM) recently gained acceptance in the essential diagnosis and treatment of hypertension in pediatric patients (Reference 11). It is most simply defined as the repeated measurement of BP in the outpatient setting while the patient is participating in normal daily living activities, including sleep (Reference 35). Pediatric patients may have dramatically different BP readings in a physician's office compared with BP readings in everyday ambulatory settings. Such patients meet the defining criteria for white-coat hypertension. However, pediatric patients who are normotensive in the office and hypertensive outside are considered to have masked hypertension. Techniques such as ABPM may reveal the presence of either diagnosis (Reference 11). According to the ESH and the AHA, ABPM is effective in detecting white-coat hypertension, masked hypertension, and differences in nocturnal BP as well as in differentiating between primary and secondary hypertension in pediatric patients (References 11, 35). The ESH recommends 24-hour ABPM to confirm or disprove suspected hypertension in patients with certain comorbidities such as diabetes, renal disease, or solid-organ

Table 2. Classification of Hypertension in Children and Adolescents, with Measurement Frequency and Therapy Recommendations

Classification	SBP or DBP Percentile*	Frequency of BP Measurement	Therapeutic Lifestyle Changes	Pharmacologic Therapy
Normal	<90th	Recheck at next scheduled physical examination	Encourage healthy diet, sleep, and physical activity	—
Prehypertension	90th to <95th or if BP exceeds 120/80 even if <90th percentile up to <95th percentile**	Recheck in 6 months	Weight-management counseling if overweight; introduce physical activity and diet management***	None unless compelling indications such as chronic kidney disease, diabetes mellitus, heart failure, or left ventricular hypertrophy exist
Stage I Hypertension	95th-99th percentile plus 5 mmHg	Recheck in 1–2 weeks or sooner if the patient is symptomatic; if persistently elevated on two additional occasions, evaluate or refer to source of care within 1 month	Weight-management counseling if overweight; introduce physical activity and diet management***	Initiate therapy based on clinical indications or other compelling indications (as shown above) exist
Stage II Hypertension	>99th percentile plus 5 mmHg	Evaluate or refer to source of care within 1 week or immediately if the patient is symptomatic	Weight-management counseling if overweight; introduce physical activity and diet management***	Initiate therapy****

*For sex, age, and height measured on at least three separate occasions; if systolic and diastolic categories are different, categorize by the higher value.
**This occurs typically at 12 years old for SBP and at 16 years old for DBP.
***Parents and children trying to modify the eating plan to the Dietary Approaches to Stop Hypertension Study eating plan could benefit from consultation with a registered or licensed nutritionist to get them started.
****More than one drug may be required.
BP = blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
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transplantation and in patients undergoing treatment of refractory hypertension (Reference 11). Complementary to the ESH recommendations, the AHA recently released an official scientific statement regarding the use of ABPM in pediatric patients to guide the diagnosis and treatment of hypertension (Reference 35). In addition, the AHA has published recommended indications for ABPM use in pediatric patients (Box 2), together with normal pediatric ABPM values for girls and boys stratified by age (5–16 years only) and height (120–175 cm only) (Reference 35).

Box 2. Indications for ambulatory blood pressure measurement.

- Confirm the diagnosis of hypertension.
- Assess blood pressure variability.
- Evaluate pharmacologic therapy effectiveness.
- More accurately evaluate blood pressure in chronic disease states.

Clinical Presentation

Children with hypertension may have varying underlying etiologies upon presentation, categorized as primary (essential) or secondary hypertension. Primary hypertension is defined as hypertension without a known cause, whereas secondary hypertension can be directly linked to a known underlying disorder (e.g., coarctation of the aorta) (Reference 10). Although primary hypertension is the most common form of hypertension in adults, the incidence of secondary hypertension in pediatric patients highly outweighs that of primary hypertension (Reference 10). The differences between primary and secondary hypertension in pediatric patients will be described in this section.

Primary Hypertension

Although primary hypertension is relatively uncommon with respect to the distribution of hypertension in pediatric patients as a whole, more attention has been drawn to primary hypertension in children and adolescents because pediatric hypertension may track into adulthood (References 5–9). The concept of tracking when referring to hypertension is illustrated by the likelihood that children who develop hypertension are more likely to be hypertensive in their adult years, thus potentially increasing future risks of individually developing serious cardiovascular disease (References 5–10). The incidence of primary hypertension has been recognized as being on the rise in children, which explains the 4th Report's recommendation for clinicians to increase the frequency of BP screening early in life (Reference 10). Because essential hypertension does not present with obvious clinical signs and symptoms, the disease has the potential to be undiagnosed for months to years and is known as a "silent killer."

Secondary Hypertension

Unlike primary hypertension, elevated BP in children is typically associated with a directly related underlying disorder. The most common etiologies of childhood hypertension occur secondary to renal/urological diseases or coarctation of the aorta (Reference 36). An underlying etiology should be ruled out for every hypertensive patient, especially when very young children, youths with stage II hypertension, or children with severe hypertension and clinical signs of end-organ damage (hypertensive emergencies) present with a confirmed diagnosis of hypertension (Reference 10). A comprehensive list of etiologies of pediatric hypertension is shown in Table 3 (Reference 37).

When ruling out secondary hypertension in children, the 4th Report recommends checking BP in both arms as well as one leg (Reference 10). The rationale is to confirm previously measured hypertensive states and potentially detect vascular abnormalities such as coarctation of the aorta (Reference 38). Children with coarctation will have decreased lower extremity BP, compared with arm measurements, because of impaired blood flow to the legs (Reference 38). In addition to impaired lower extremity blood flow, the BP measured in the left arm may be lower than that in the right arm if the coarctation is proximal to the left subclavian artery (Reference 39). Although expert recommendations guide clinicians to measure two upper extremity BPs followed by one measurement in the legs, many clinicians recommend one upper extremity reading and one lower measurement, especially in younger children, to prevent falsely high measurements caused by discomfort and agitation from repeated BP measurements.

Management of Pediatric Hypertension

Therapeutic Goals

The goals of therapeutic management are highly dependent on the clinical presentation and severity of hypertension. For example, BP reduction is needed much more urgently in a patient who presents with hypertensive crisis compared with a patient with stage I essential hypertension. This section will review goals of antihypertensive therapies as well as appropriate management strategies of pediatric hypertension, including lifestyle modifications and pharmacologic therapy.

Lifestyle Modifications

Lifestyle modifications to treat pediatric hypertension include exercise, weight loss, and stress reduction. The goal of using such lifestyle modifications to treat pediatric hypertension is to lower BP within an acceptable range without the use of medications. When lifestyle modifications do not achieve this goal or when medication is required as a first-line treatment option, lifestyle modifications should be combined with pharmacotherapy. Exercise is a recommended nonpharmacologic therapy for children and adolescents with essential hypertension and may be used as primary or adjunctive treatment (Reference 10). The AHA currently recommends that children 2 years or older participate in at least 60 minutes of developmentally appropriate, moderate-intensity physical activity each day of the week (Reference 40). Many studies have shown that exercise programs lower both SBP and DBP in children (References 41–45). The common factor shown to reduce BP is aerobic exercise, whereas resistance training alone has not had a therapeutic effect (References 41–45). The discontinuation of aerobic activity results in the return of BP to pre-exercise values, so continued commitment to an exercise routine is recommended (References 41–44).

Table 3. Common Causes of Pediatric Hypertension

Neonates (0–30 days)	Infant to 6 Years	6–10 Years	10 Years to Adolescence
Renovascular ▪ Renal artery thrombosis ▪ Renal venous thrombosis Renal parenchymal ▪ Obstructive uropathy ▪ Renal dysplasia ▪ Polycystic kidney disease Neoplasia ▪ Neuroblastoma ▪ Mesoblastic nephroma Cardiovascular ▪ Coarctation of the aorta Endocrine ▪ Hyperthyroidism Drugs ▪ Corticosteroids ▪ Phenylephrine eyedrops ▪ Theophylline ▪ Caffeine ▪ Maternal drug use (e.g., cocaine) Other ▪ Bronchopulmonary dysplasia ▪ Intracranial hemorrhage ▪ Seizures ▪ Extracorporeal membrane oxygenation ▪ Volume overload ▪ Abdominal wall defect closure	Renal parenchymal ▪ Pyelonephritis ▪ Glomerulonephritis ▪ Hemolytic uremic syndrome ▪ Renal dysplasia ▪ Polycystic kidney disease ▪ Obstructive uropathy ▪ Takayasu disease ▪ End-stage renal disease ▪ Renal artery stenosis Neoplasia ▪ Wilms tumor Essential hypertension Cardiovascular ▪ Coarctation of the aorta Endocrine ▪ Corticosteroid excess ▪ Pheochromocytoma Central nervous system ▪ Space-occupying lesions Drugs ▪ Amphetamines ▪ Phenylephrine eyedrops ▪ Glucocorticoids ▪ Mineralocorticoids Other ▪ Poisonings (lead, mercury)	Renal artery stenosis Renal parenchymal ▪ Glomerulonephritis ▪ Reflux nephropathy ▪ Pyelonephritis ▪ Vasculitis Endocrine ▪ Corticosteroid excess ▪ Hyperaldosteronism (adenoma, hyperplasia) ▪ Pheochromocytoma Essential hypertension	Essential hypertension Renal parenchymal disease ▪ Glomerulonephritis ▪ End-stage renal disease ▪ Pyelonephritis

Information from Reference 37, with permission.

In addition to exercise, weight loss is an essential lifestyle modification to use when obesity and hypertension coexist (Reference 46). Not only does weight reduction have a BP-lowering effect, but it also minimizes other cardiovascular risk factors such as dyslipidemia and insulin resistance (Reference 10). Diet is an essential part of an adequate weight-loss program, especially in hypertensive patients (References 10, 47). Salt restriction and other healthy eating habits are recommended for hypertensive adults and children alike (Reference 47). Because excess sodium intake is directly related to hypertension, the AHA has developed maximum daily sodium intake recommendations (Table 4) for pediatric patients to curb sodium overindulgence (Reference 48).

Together with exercise and weight loss, stress reduction may be a key nonpharmacologic intervention to help reduce BP because it has been identified as an environmental factor that may lead to the development of essential hypertension (Reference 37). Although concrete recommendations do not exist regarding the modality in which stress should be reduced in children to prevent or reduce high BP, stress reduction is still thought of as an important potential intervention in pediatric patients (Reference 10).

Approach to Pharmacologic Therapy

Because of the potential cardiovascular consequences of prolonged hypertension and the tracking phenomenon of BP into adulthood, BP reduction in children with hypertension is now regarded as an important therapeutic goal to prevent complications associated with the disease (Reference 10). The 4th Report clearly defines the indications for pharmacologic treatment of hypertension in children as the following clinical cases: symptomatic hypertension, secondary hypertension, hypertensive target-organ damage, failure of nonpharmacologic BP reduction measures, and type 1 and 2 diabetes mellitus (Reference 10). The goals of pharmacologic therapy differ depending on the severity of hypertension and the coexistence of other risk factors and comorbidities. The 4th Report defines BP reduction goals with specific indications, listed in Table 5 (Reference 10). Although adult studies typically aim to reveal differences in morbidity and mortality between treatment groups through long-term follow-up studies, similar high-quality treatment data are unavailable in pediatric patients. Because clinical trials linking improved outcomes to specific antihypertensive agents are nonexistent in pediatric patients, adult data may be extrapolated to this patient population to guide treatment.

Initiation of an antihypertensive agent in a pediatric patient typically follows a stepwise pattern. The recommended strategy for treating pediatric hypertension is to start with low doses and titrate upward slowly on the basis of achieved goal BP (Table 5) and tolerability of the drug (Reference 10). Drug titration should be halted or another agent should be considered for primary or adjunct therapy when the highest recommended dose is reached (Reference 10). When adverse effects develop, medication doses may need to be reduced or discontinued altogether, and another agent may need to be considered (Reference 10). Table 6 provides a comprehensive list of medication doses, including typical pediatric dosing ranges and considerations for antihypertensive agents.

Pharmacologic Therapy

Antihypertensive drug classes used in children consist of ACE inhibitors, ARBs, calcium channel blockers (CCBs), diuretics (loop, thiazide, and potassium-sparing diuretics), β-adrenergic receptor antagonists, centrally acting sympatholytic agents, peripheral adrenergic antagonists, and direct-acting vasodilators. Although adult prescribing patterns typically aim to lower morbidity and mortality by following evidence-based guidelines, such data are unavailable to guide therapy in children. Therefore, the treatment goal for hypertension in children is simply to lower BP within the range of BP norms for age, sex, and height while limiting adverse events.

Table 4. Maximum Daily Recommended Sodium Intake

Age (years)	Sodium (mg)
1–3	1500
4–8	1900
9–13	2200
14–18	2300

Adapted with permission from Reference 48.

Table 5. Blood Pressure Treatment Goals

Comorbidities	Blood Pressure Reduction Goal
Uncomplicated, primary, no target organ damage	< 95th percentile
Chronic renal disease, diabetes, or hypertensive target organ damage	< 90th percentile

Information from Reference 10.

ACE Inhibitors

Mechanism/Use

The therapeutic effect of ACE inhibitors in children is achieved by inhibiting the conversion of AT I to AT II, a potent vasoconstrictor (Reference 49). Because AT II facilitates sympathetic activity, ACE inhibitors reduce BP by decreasing systemic vascular resistance (SVR) (Reference 49). In addition, because AT II promotes aldosterone and antidiuretic hormone release while causing vasoconstriction of the efferent arterioles of the kidney, ACE inhibitors decrease intravascular volume by promoting diuresis and natriuresis (Reference 49). Angiotensin-converting enzyme inhibitors also prolong the half-life of the vasodilator bradykinin by inhibiting its metabolism (Reference 49). Although ACE inhibitors have been shown to prevent the cardiac and vascular remodeling associated with chronic hypertension and heart failure in adults, their use for this purpose currently can only be extrapolated to children because pediatric clinical data are unavailable.

Pediatric Pharmacokinetics

Captopril is probably one of the most widely used ACE inhibitors in children because of its short half-life, making it an easily titratable drug. This property also enhances safety to the patient and security to the clinician when initiating the drug because its BP-lowering effects will be short-lived if hypotension occurs. This is important to consider in children, especially infants and neonates, because ACE inhibitor–induced hypotension is more likely to be seen in this age group (Reference 37). Risks of hypotension in this patient population must be respected; thus, low initial doses and slow upward

Table 6. Medications Used in Pediatric Hypertension[a]

Class	Drug	Dose	Interval	Liquid Preparation Available?	Adverse Effects	Removed by Dialysis?	Adjustment for Organ Dysfunction	Notes
ACE inhibitor	Captopril	Initial: Preterm neonates: 0.01 mg/kg/dose < 6 months: 0.1 mg/kg/dose ≥ 6 months: 0.3–0.5 mg/kg/dose Max: 6 mg/kg/day	TID	Yes	Angioedema Cough Dysgeusia Hyperkalemia Neutropenia Orthostatic hypotension Rash	C - Yes HPD - Likely PD - No	Renal	Neonates and infants may need lower initial doses and require slow titration.[b] Contraindicated in pregnancy[b] Avoid in patients with bilateral renal artery stenosis.[b] Monitor serum potassium and creatinine periodically.[b] Incidence of cough is very low in pediatric patients.[b]
	Enalapril	Initial: 0.08 mg/kg/day up to 5 mg Max: 0.6 mg/kg/day up to 40 mg	Daily–BID	Yes		C - Yes HPD - Likely PD - Yes	Renal	
	Lisinopril	Initial: 0.07 mg/kg/day up to 5 mg Max: 0.6 mg/kg/day up to 40 mg	Daily	Yes		C - Yes HPD - Likely PD - ND	Renal	
ARB	Irbesartan	6–12 years: 75–150 mg/day ≥ 13 years: 150–300 mg/day	Daily	No	Cough Hyperkalemia Orthostatic hypotension	C - No HPD - ND PD - ND	No - Caution in renal impairment	Monitor serum potassium and creatinine periodically.[b] Contraindicated in pregnancy[b] Incidence of cough is very low in pediatric patients.[b] Use close blood pressure monitoring to guide adjustment for renal or hepatic dysfunction. Not recommended in children if creatinine clearance is ≤ 30 mL/minute[b] Use of valsartan in children younger than 6 years is not recommended.[b] Valsartan oral suspension has increased bioavailability compared with tablet formulation.[b]
	Losartan	Initial: 0.7 mg/kg/day up to 50 mg Max: 1.4 mg/kg/day up to 100 mg	Daily	Yes		C - No HPD - No PD - No	Not recommended in severe renal or hepatic impairment	
	Olmesartan	1–5 years and ≥ 5 kg: 0.3 mg/kg/day Max: 0.6 mg/kg/day 20 to < 35 kg: 10 mg/day up to 20 mg ≥ 35 kg: 20 mg/day up to 40 mg	Daily	Yes		C - No HPD - No PD - Unlikely	No	
	Valsartan	6–16 years: 1.3 mg/kg/day up to 40 mg/day Max: 2.7 mg/kg/day up to 160 mg/day	Daily	Yes		C - No HPD - ND PD - Unlikely	Renal Use caution in hepatic impairment.	
α- and β-antagonists	Labetalol	Initial: 1–3 mg/kg/day Max: 10–12 mg/kg/day up to 1,200 mg	BID	Yes	Bradycardia Bronchospasm Hyperkalemia	C - No HPD - ND PD - No	Potential reduction needed in hepatic impairment	

(Continued)

Table 6. Medications Used in Pediatric Hypertension[a] *(Continued)*

Class	Drug	Dose	Interval	Liquid Preparation Available?	Adverse Effects	Removed by Dialysis?	Adjustment for Organ Dysfunction	Notes
β-Antagonist	Atenolol	Initial: 0.5–1 mg/kg/day Max: 2 mg/kg/day up to 100 mg	Daily–BID	Yes	Bradycardia Bronchospasm Drowsiness Exercise intolerance Fatigue Heart block Hypoglycemia Lethargy	C - Yes HPD - Likely PD - No	Renal	Use caution in children with diabetes because β-blockers prevent signs and symptoms of hypoglycemia.[b] Hypoglycemia caused by β_2-blockade, which inhibits glycogenolysis in the liver and glucagon release from the pancreas[b] Use caution in children with asthma with nonselective agents, although not an absolute contraindication.[b] Propranolol is the most lipophilic and has the highest propensity to cause CNS-related adverse effects.[b]
	Metoprolol	Initial: 1–2 mg/kg/day Max: 6 mg/kg/day up to 200 mg	BID	Yes		C - Yes HPD - Likely PD - ND	Potential reduction needed in hepatic impairment	
	Propranolol	Initial: 0.5–2 mg/kg/day Max: 4 mg/kg/day up to 640 mg	BID–four times/day	Yes[c]		C - No HPD - Unlikely PD - No	Potential reduction needed in hepatic impairment	
CCBs	Amlodipine	1–5 years: 0.05–0.1 mg/kg/day 6–17 years: 2.5–5 mg/day	Daily–BID	Yes	Constipation Dizziness Flushing Palpitations Tachycardia	C - No HPD - Unlikely PD - No	No - Monitor closely in hepatic impairment.	Use with caution in patients younger than 1 year.[b] Felodipine and nifedipine (extended release only) cannot be crushed or chewed.[b]
	Felodipine	Initial: 2.5 mg/day Max: 10 mg/day	Daily	No		C - No HPD - Unlikely PD - Unlikely	No - Monitor closely in hepatic impairment.	
	Isradipine	Initial: 0.15–0.2 mg/kg/day Max: 0.8 mg/kg/day up to 20 mg/day	TID–four times/day	Yes		C - No HPD - Unlikely PD - No	No - Monitor closely in hepatic or renal impairment.	
	Nifedipine (extended release)	Initial: 0.25–0.5 mg/kg/day Max: 3 mg/kg/day up to 180 mg/day	Daily–BID	No		C - No HPD - Unlikely PD - No	Potential reduction needed in hepatic impairment	

Class	Drug	Dose	Interval	Liquid Preparation Available?	Adverse Effects	Removed by Dialysis?	Adjustment for Organ Dysfunction	Notes
Central α-agonist	Clonidine	Initial: 5–10 mcg/kg/day Max: 25 mcg/kg/day OR 0.9 mg/day	BID–TID	Yes	Bradycardia Constipation Drowsiness Dry mouth Orthostatic hypotension Rebound hypertension Sedation	C - No HPD - ND PD - No	Renal	Transdermal dose is equivalent to total daily oral dose. Patches should not be cut.[b] Should not be abruptly discontinued because of risks of rebound hypertension.[b]
	Guanfacine	≥ 12 years: 1 mg Max: 2 mg	QHS			C - No HPD - ND PD - No	Use with caution in renal or hepatic impairment.	
	Methyldopa	Initial: 2.5 mg/kg/dose Max: 65 mg/kg/day OR 3 g/day	BID–four times/day	Yes		C - Yes HPD - Likely PD - Yes	Renal	
Direct renin inhibitor	Aliskiren	Initial: 1.7–2 mg/kg/day Max: 4–4.2 mg/kg/day up to 300 mg	Daily	No	Angioedema Diarrhea Dizziness Headache Hyperkalemia	C - ND HPD - ND PD - ND	No - Use with caution in renal impairment.	Contraindicated in pregnancy[b] Contraindicated in adult patients with diabetes or moderate to severe renal impairment while taking ACE inhibitors or ARBs[b] Reported only in a case series of four patients with chronic kidney disease and in a survey of 10 patients aged 4–17 years[b] Studies are currently enrolling patients, but safety and efficacy data are not known. Use caution when using in pediatric patients.[b]
Diuretics								
Loop	Furosemide	Initial: 0.5–2 mg/kg/dose Max: 6 mg/kg/dose	Daily–four times/day	Yes[c]	Hypocalcemia Hypochloremic metabolic alkalosis Hypokalemia Hypomagnesemia Hypovolemia Ototoxicity	C - No HPD - Unlikely PD - Unlikely	No	Risk and severity of ototoxicity are directly related to high doses.[b]
Thiazide	HCTZ	Initial: 1 mg/kg/day Max: 3 mg/kg/day up to 50 mg	Daily	Yes	Dyslipidemia Hypochloremic metabolic alkalosis Hyperglycemia Hypokalemia Hypomagnesemia Hyponatremia Hypovolemia Hyperuricemia	C - No HPD - ND PD - Unlikely	No	Mechanism behind dyslipidemia and hyperglycemia remains unclear.[b] May be ineffective in patients with poor renal function.[b]

(Continued)

Table 6. Medications Used in Pediatric Hypertension[a] *(Continued)*

Class	Drug	Dose	Interval	Liquid Preparation Available?	Adverse Effects	Removed by Dialysis?	Adjustment for Organ Dysfunction	Notes
K^+ sparing	Amiloride	Initial: 0.4–0.625 mg/kg/day up to 20 mg	Daily	Yes	Gynecomastia (only spironolactone) Hyperkalemia Metabolic acidosis	C - ND HPD - ND PD - ND	Renal	Avoid use in patients with severe renal dysfunction.[b]
	Spironolactone	Initial: 1 mg/kg/day Max: 3.3 mg/kg/day up to 100 mg	Daily–BID	Yes		C - Unlikely HPD - ND PD - Unlikely	Renal	
	Triamterene	Initial: 1–2 mg/kg/day Max: 3–4 mg/kg/day up to 300 mg	BID	No		C - ND HPD - ND PD - ND	Renal	
Peripheral α-antagonist	Doxazosin	Initial: 1 mg/day Max: 4 mg/day	Daily	No	Dizziness Drowsiness Fatigue Headache Muscle weakness Orthostatic hypotension	C - No HPD - ND PD - No	Use with caution in hepatic impairment.	Usually not first-line agents — usually used in resistant hypertension[b]
	Prazosin	Initial: 0.05–0.1 mg/kg/day Max: 0.5 mg/kg/day	TID	Yes		C - No HPD - Unlikely PD - No	No	
	Terazosin	Initial: 1 mg/day Max: 20 mg/day	Daily	No		C - No HPD - Unlikely PD - No	No	
Vasodilator	Hydralazine	Initial: 0.75 mg/kg/day Max: 7.5 mg/kg/day up to 200 mg	Four times/day	Yes	Dizziness Hypertrichosis (minoxidil only) Orthostatic hypotension Sodium and water retention RAAS activation Reflex tachycardia Vivid dreams	C - No HPD - ND PD - No	Renal	Usually not first-line agents — usually used in resistant hypertension or in hypertensive crisis[b] Hydralazine may cause rebound hypertension by RAAS activation.[b]
	Minoxidil	Initial: 0.04–0.07 mg/kg/dose Max: 50–100 mg/dose	Daily–TID	Yes		C - Yes HPD - Likely PD - Yes	No	

[a]All agents may cause hypotension.
[b]Information from References 10, 37, 49–59, 65, 68, 69, 75, 79–95, 111–119.
[c]Compound is commercially available.
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BID = twice daily; C = conventional hemodialysis (KUf ≤ 8 mL/hour/mm Hg); CCB = calcium channel blocker; CNS = central nervous system; HCTZ = hydrochlorothiazide; HPD = high permeability dialysis (KUf > 8 mL/hour/mm Hg); Max = maximum; ND = no data available; PD = peritoneal dialysis; QHS = every night; RAAS = renin-angiotensin-aldosterone system; TID = three times/day.

titration are recommended to avoid these risks, particularly in neonates and infants. For unknown reasons, neonates and infants have an increased sensitivity to ACE inhibitors. Proposed mechanisms include, but are not limited to, higher renin concentrations, developing kidneys, and decreased hepatic drug metabolism in this age group (Reference 37). Angiotensin-converting enzyme inhibitors with longer half-lives, such as enalapril and lisinopril, are also used in children (Reference 37). Advantages include increased adherence and improved quality of life with once- or twice-daily administration.

Both captopril and enalapril are extensively metabolized and excreted into the urine (Reference 49). Enalapril, which is actually a prodrug, must be metabolized by the liver to its active form, enalaprilat, before it exhibits antihypertensive effects (Reference 49). Lisinopril is not hepatically metabolized and is primarily excreted in the urine as unchanged drug (Reference 49).

Adverse Effects

Angiotensin-converting enzyme inhibitors are generally well tolerated in children, making them an attractive therapeutic option. Many adverse effects caused by ACE inhibitors, particularly ACE inhibitor–induced cough, occur rarely in children compared with the rate of occurrence in adults (References 50–52).

AT II Receptor Antagonists

Mechanism/Use

Because AT II is generated by other pathways in addition to the ACE, ARBs were developed to block the final step in this neurohormonal pathway—the binding of AT II to AT_1-receptors (Reference 24). By antagonizing this receptor, ARBs cause vasodilation, aldosterone antagonism, reduction in sympathetic activity, and renal efferent arteriole relaxation (Reference 24). Unlike ACE inhibition, ARBs do not affect the metabolism of bradykinin (Reference 24). Because elevated bradykinin concentrations cause vasodilation, however, this may be a drawback to ARB therapy.

Pediatric Pharmacokinetics

Many ARBs have been reported to be used in pediatric patients, with several studies recently published at the time of this writing (References 53–58). Pharmacokinetic properties of ARBs in pediatric patients vary depending on the agent used (References 54, 56–58). Onset of action typically occurs within 1–2 hours. Most ARBs are metabolized from an inactive form to an active metabolite, with olmesartan metabolism occurring in the gut (References 54, 56, 58). Angiotensin receptor blockers are eliminated primarily through the fecal route as well as the urine (References 54, 56, 58). The half-lives of ARBs are prolonged (6–15 hours), allowing once-daily dosing (References 54, 56, 58). Data in young children (younger than 6 years) are relatively scant, with most available data representing the use of valsartan (References 53, 54).

Adverse Effects

In pediatric randomized controlled trials, ARBs have a pediatric adverse effect profile similar to placebo (References 53, 57, 58). The reported adverse effects are similar to those of ACE inhibitors, and the class of ARBs as a whole has been reported to be well tolerated in children, causing minimal episodes of hypotension (References 53–58).

Direct Renin Inhibitors

Mechanism/Use

Renin inhibition is not currently an attractive therapeutic option for pediatric hypertension. Aliskiren, the only U.S. Food and Drug Administration–approved direct renin inhibitor, prevents the production of AT I and therefore reduces AT II concentrations, causing vasodilation. As of this writing, the use of aliskiren had only been reported in four pediatric patients with chronic kidney disease, indicating the paucity of important clinical data to guide prescribers on safe and effective use (Reference 59). Hope is on the horizon, however, because a pharmacokinetic study of children aged 6–17 years is already complete (not yet published). In addition, a follow-up study evaluating safety and efficacy is enrolling patients (References 60, 61).

Pediatric Pharmacokinetics

Very little is known about the pharmacokinetics of aliskiren in pediatric patients because of the lack of available literature (Reference 59).

Calcium Channel Antagonists

Mechanism/Use

Calcium channel antagonists are being used in the treatment of pediatric hypertension, despite the paucity of clinical data establishing the safety and efficacy of their use (Reference 62). The classification of CCBs, which identifies drugs in this class as dihydropyridines and non-dihydropyridines, is based on relative cardiac/vascular activity. Cardiac and vascular smooth muscle both rely on intracellular calcium for contraction. By blocking the influx of extracellular calcium, CCBs help decrease SVR and cardiac conduction. At therapeutic doses, the dihydropyridines are relatively safe to use in all age ranges and are the most useful class in the treatment of pediatric hypertension (Reference 62). Their high affinity for vascular calcium channels results in a reduction in BP by decreasing SVR through vasodilation (Reference 62). Non-dihydropyridine CCBs are generally recommended to be avoided in patients

younger than 1 year because the inhibition of AV node conduction may cause potent negative inotrope effects and thus can be fatal in young children (References 10, 62–64). Although JNC VII does not recommend the use of a CCB as a single agent for adult hypertension, the 4th Report includes CCBs as an acceptable first-line option in pediatric patients (References 10, 33).

Pediatric Pharmacokinetics

Amlodipine has seldom been studied in children; however, case reports suggest those younger than 6 years require higher doses per kilogram and even twice-daily dosing (Reference 65). Nifedipine is used for pediatric hypertension, but most of the available literature discusses its use for hypertensive urgencies, which will be discussed later (Reference 65). All CCBs are hepatically metabolized and do not require adjustment in the presence of renal dysfunction. Amlodipine is the dihydropyridine with the highest vascular selectivity, greatest oral bioavailability, and longest half-life, allowing once-daily dosing for chronic hypertension.

β-*Adrenergic Receptor Antagonists*

Mechanism/Use

Blood pressure reduction with β-adrenergic antagonists (β-blockers) is achieved by reducing cardiac output through negative inotropic and chronotropic effects (References 66, 67). The receptor specificity and relative cardioselectivity vary between β-blockers. Atenolol and metoprolol are very cardioselective (except at high doses), antagonizing only β_1-receptors, whereas propranolol blocks β_1 and β_2. This additional β_2-blockade may result in pulmonary cross-reactivity leading to bronchoconstriction and asthma exacerbations; however, the incidence in pediatric patients is minimal (Reference 66). In addition to β_1- and β_2-blockade, carvedilol possesses α_1-receptor activity, causing a reduction in SVR.

Pediatric Pharmacokinetics

The pharmacokinetics as well as receptor specificity vary widely between β-blockers. All are lipophilic enough to cross the blood-brain barrier and thus have the ability to cause drowsiness and fatigue (References 66, 67). Propranolol shows the most rapid onset of action (1–2 hours) and has the shortest half-life (4.5 hours), whereas atenolol and metoprolol typically take longer to take effect (3 hours) and have a longer elimination half-life (8 hours). Metoprolol and propranolol are both hepatically metabolized and therefore need not be adjusted in renal dysfunction (Reference 67). Atenolol, however, undergoes minimal hepatic metabolism and is highly eliminated through the urine, leaving patients with renal dysfunction at a higher risk of drug accumulation and accompanying adverse effects (Reference 67).

Diuretics

The 4th Report includes diuretics as an option for first-line antihypertensive therapy in children (Reference 10). In contrast to JNC VII, which recommends a thiazide diuretic as first-line therapy for most adult patients, the 4th Report does not single out a specific drug or drug class for clinicians to target as first-line therapy in children and adolescents (References 10, 33). By reducing intravascular volume and peripheral vascular resistance, diuretics have been shown to decrease BP (Reference 37). They may be particularly useful in patients who require several drugs to control hypertension or who have considerable sodium and water retention.

Mechanism/Use

LOOP DIURETICS

Loop diuretics are the most powerful diuretics that may also have effects on hemodynamics. After reaching the tubular lumen of the nephron, their inhibition of the $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending loop of Henle causes increased sodium concentrations in the distal tubule, thus promoting diuresis and natriuresis (Reference 70). Loop diuretics also potentiate the production of prostaglandins in the kidneys, leading to enhanced renal blood flow. As a whole, loop diuretics have no significant effect on hemodynamics, and they are generally not considered potent antihypertensive agents in children (Reference 70). Furosemide is the most commonly used loop diuretic in children. Other loop diuretics, such as torsemide and bumetanide, are not routinely used in the management of hypertension in children (References 10, 71–74).

THIAZIDE/THIAZIDE-LIKE DIURETICS

Thiazide diuretics are recommended by JNC VII as a first-line antihypertensive agent in most adults, and they are used in children as well (Reference 33). By inhibiting the Na^+/Cl^- transporter in the distal tubule, thiazide and thiazide-like diuretics produce mild diuresis and natriuresis by inhibiting about 5% of total sodium reabsorption, showing about one-fifth the diuretic capability of loop diuretics (Reference 75). Although their diuretic actions are mild, the proposed mechanism behind their hemodynamic effects is a reduction in SVR by direct vasodilation caused by vascular potassium channel activation (References 75–77). Commonly prescribed thiazide diuretics in children include chlorothiazide and hydrochlorothiazide, whereas thiazide-like diuretics include chlorthalidone and metolazone.

POTASSIUM-SPARING DIURETICS

Potassium-sparing diuretics all work to promote diuresis while conserving potassium depletion; however, spironolactone shows slight mechanistic differences compared with amiloride and triamterene. Spironolactone antagonizes aldosterone by competing for binding sites at the distal segment of the distal tubule, causing increased Na^+ and H_2O excretion into the urine. Its potassium-sparing effects are produced by the inhibition of aldosterone-sensitive sodium reabsorption (Reference 78). By inhibiting this mechanism, fewer potassium and hydrogen ions are excreted in the urine (Reference 78). Amiloride and triamterene, however, directly inhibit sodium channels in the distal convoluted tubule and the collecting duct, thus reducing the activity of the sodium/potassium transporter in the distal renal tubule to produce potassium-sparing diuresis independently of aldosterone (Reference 78).

Centrally Acting Sympatholytic Agents

Mechanism/Use

α_2-Adrenergic receptor activation in the brain decreases BP through sympathetic tone reduction (Reference 86). Drugs that show this pharmacologic activity include clonidine, guanabenz, guanfacine, and methyldopa (Reference 86). Clonidine is the most commonly prescribed α_2-agonist for the treatment of pediatric hypertension. Guanfacine and methyldopa are also used, but less often (Reference 86). Guanfacine and clonidine are also used for other indications such as attention-deficit/hyperactivity disorder (References 87, 88). Clonidine has shown utility in adjunctive analgesia and prevention of withdrawal symptoms associated with opioid weans as well (References 89, 90).

α_2-Adrenergic receptor agonists are typically not considered first-line therapy for hypertension in adults because of the lack of long-term morbidity and mortality data. Use in pediatric patients is low for the same reasons and may be avoided because of the incidence of adverse effects and subsequent reduction in quality of life. For these reasons, α_2-adrenergic agonists are typically reserved as adjunctive agents to be used in refractory hypertension or single-dose agents for hypertensive emergencies while intravenous agents are being prepared (Reference 86).

Pediatric Pharmacokinetics

The onset of action for guanfacine and methyldopa are 1.5–4 hours and 2 hours, respectively (Reference 86). Their duration of action, however, varies widely, with guanfacine showing a half-life of about 17 hours (allowing once-daily dosing), compared with 1.7 hours (up to four times/day dosing) for methyldopa (Reference 86). Both drugs are eliminated primarily by the kidneys (Reference 86). The pharmacokinetic profile of clonidine will be reviewed in detail in the hypertensive crisis section later in the chapter.

Peripheral Adrenergic Antagonists and Direct Vasodilators

Mechanism/Use

These agents are typically used as adjunctive medications for refractory hypertension and are not often selected as first-line agents. Selective α_1-receptor blockade causes peripheral vasodilation and a subsequent reduction in BP. Doxazosin, prazosin, and terazosin make up the α_1-receptor blocker drug class. Minoxidil and hydralazine are direct vasodilators that are also used in the treatment of hypertensive urgencies (References 37, 91–95).

The prescribing of both drug classes for childhood hypertension has dwindled and is associated with the potential for adverse effects (Reference 37). In addition, adult data showing a reduction in morbidity and mortality with their use are nonexistent and have been linked to increases in cardiovascular morbidity, thus preventing pediatric extrapolation and halting subsequent increases in prescribing patterns (Reference 96).

Pediatric Pharmacokinetics

The pediatric pharmacokinetic profile of minoxidil and hydralazine will be reviewed in the hypertensive crisis section later in the chapter.

Monitoring Therapeutic Outcomes

The frequency and intensity of monitoring in patients with pediatric hypertension are highly reliant on the severity of illness at presentation and the presence of underlying disease states. Table 2 highlights the recommended frequency of BP measurement according to severity of hypertension (Reference 10).

Hypertensive Crises

Pediatric hypertensive crises markedly increase the risks of morbidity and mortality, prompting immediate clinical attention and necessitating emergency treatment (References 37, 91). Despite many years of available therapeutic treatment options, a paucity of robust pediatric clinical literature exists. Randomized controlled trials enrolling patients with pediatric hypertensive emergencies are nonexistent. This forces clinicians to make empiric clinical decisions forged from extrapolated adult data and small pediatric observational studies. A sound knowledge base of pediatric pharmacology and pathophysiology is needed in conjunction with a thorough understanding of the adult and pediatric clinical literature to guide clinical decision-making.

Definitions and Clinical Presentation

Both hypertensive emergencies and urgencies are considered types of hypertensive crises. Hypertensive urgency is defined as severely elevated BP without signs

and symptoms of end-organ dysfunction (Reference 10). A hypertensive emergency, however, is severely elevated BP presenting with end-organ damage (Reference 10). An example of the difference between the two diagnoses includes a patient with severely elevated BP and corresponding seizures (hypertensive emergency) compared with a patient with an equivalently elevated BP and less severe symptoms, such as a severe headache (hypertensive urgency) (References 97, 98).

Pediatric hypertensive crises present in a variety of ways, but by definition, all cases have severely elevated BP. Exceeding stage II hypertension in severity, both hypertensive urgencies and emergencies require immediate pharmacologic intervention to reduce BP, even though their clinical presentation differs. Debate is ongoing regarding the necessity to differentiate between the two definitions because each diagnosis equally requires prompt medical intervention with the same pharmacologic agents and treatment strategies (Reference 91). Even more important than being able to differentiate between the definitions of hypertensive urgency and emergency on clinical presentation is the ability to grasp the concept that a failure to rapidly treat patients with hypertensive crisis leads to end-organ dysfunction that might eventually cause irreversible damage or death (References 37, 99). Signs and symptoms of end-organ damage may manifest as encephalopathy, seizures, intracerebral hemorrhage, facial palsy, retinopathy, acute renal failure, hematuria, congestive heart failure, and arrhythmias (References 10, 37, 91, 99–103).

Pathogenesis

As discussed at the beginning of this chapter regarding the pathogenesis of primary and secondary hypertension, hypertensive crises are also a result of the dysfunction of complex neurohormonal and hemodynamic pathways causing dangerous elevations in systemic BP (References 91, 99). Activation of the RAAS, oxidative and mechanical damage to the microvasculature, fluid overload, severe renal dysfunction, coarctation of the aorta, sympathetic overstimulation, and endothelial dysfunction all may contribute to the pathology of hypertensive crises (References 91, 99).

Pharmacologic Therapy for Hypertensive Crisis

Therapeutic Goals

Pediatric guidelines for the treatment of high BP call for controlled antihypertensive therapy in patients with hypertensive crisis (Reference 10). Goals for controlled antihypertensive therapy include a gradual BP decrease of 25% or less within the first 8 hours, followed by a deliberate and gradual lowering of BP throughout the next 40 hours (Reference 10). Final goals to aim for should include BP at the 90th percentile or less for sex, age, and height if patients present with end-organ damage or have underlying comorbidities such as diabetes or chronic renal dysfunction (Reference 10). All other patients should have their BP decreased to the 95th percentile or less (Reference 10).

Oral agents may be used for hypertensive crises in pediatric patients, but unlike medications used as rapidly titratable continuous infusions, their utility is generally limited to less severe cases such as hypertensive urgencies (References 10, 91, 94, 95, 97–110). Easily titratable continuous infusions are typically preferred because of their superior ability to tightly control BP descent, which allows a rapid reduction in BP while avoiding dangerously fast decreases (Reference 91). Table 7 highlights common intravenous agents, including pediatric dosing ranges and considerations for hypertensive crisis.

Sodium Nitroprusside

Mechanism/Use

Sodium nitroprusside (SNP) is rapidly metabolized to cyanide and nitric oxide within red blood cells, which directly vasodilate arterial and venous smooth muscle, and is considered a first-line therapeutic agent for hypertensive crises (References 66, 120). With its initial pediatric data reported in the 1970s, SNP is historically one of the most frequently used agents for hypertensive crisis in children, despite the absence of a single randomized controlled trial (Reference 121).

Pediatric Pharmacokinetics

Pharmacologic assets of SNP include a rapid onset of action (less than 60 seconds) and a short elimination half-life, allowing rapid titration of continuous infusions (Reference 66). Another benefit includes its ability to lower BP by decreasing SVR without increasing preload or causing negative inotropic effects (Reference 122).

Drawbacks of SNP administration include potential cyanide and thiocyanate toxicity in addition to tachyphylaxis associated with prolonged therapy (Reference 122). Cyanide toxicity results from enzymatic breakdown of SNP within red blood cells (References 122, 123). Humans are normally able to attenuate cyanide accumulation by forming the renally eliminated thiocyanate molecule. This is accomplished by the enzyme rhodanese in the presence of thiosulfate.

High doses, prolonged infusions, or the presence of hepatic dysfunction causes depletion of endogenous thiosulfate stores, which increases the risk of cyanide toxicity, whereas prolonged infusions and renal dysfunction may cause thiocyanate accumulation and subsequent toxicity (Reference 124). Signs and symptoms of cyanide toxicity include the following: vomiting, headache, hypotension, delirium, psychosis, weakness, muscle spasms, tachypnea, tachycardia, tinnitus, metabolic acidosis, coma, and death (References 122, 123).

Table 7. Common Intravenous Agents Used in Pediatric Hypertensive Crisis[a,b]

Drug	Mechanism of action	Initial dose	Maximal dose	Adverse effects	Adjustment for organ dysfunction	Notes
Esmolol	β_1-Antagonist	**B:** 100–500 mcg/kg **C:** 50–500 mcg/kg/hour	**B:** 500 mcg/kg **C:** 1000 mcg/kg/hour	Bradycardia Bronchospasm (potential at high doses) Hypoglycemia	No	▪ Loses β_1-selectivity at higher doses, although the dose at which it loses cardioselectivity is unknown ▪ Bolus doses as high as 1000 mcg/kg and continuous-infusion rates up to 1000 mcg/kg/minute have been reported.
Hydralazine	Direct vasodilator (arterial)	0.1–0.2 mg/kg/dose every 4–6 hours	0.6 mg/kg/dose OR 20 mg	Dizziness Headache Palpitations Reflex tachycardia Rebound hypertension	Renal	▪ May be given IV or IM ▪ May be given orally as well (0.25 mg/kg/dose every 6 hours, max: 25 mg) ▪ Activates RAAS ▪ Prolonged half-life ▪ Often used as a single dose to control hypertension while continuous agents are being prepared
Labetalol	α_1, β_1, β_2-antagonist	**B:** 0.2–1 mg/kg **C:** 0.25–1 mg/kg/hour	**B:** 20 mg **C:** 3 mg/kg/hour	Bradycardia Bronchospasm Hyperkalemia Hypoglycemia	Potential reduction needed in hepatic impairment	▪ Does not cause reflex tachycardia ▪ Longer half-life compared with other agents ▪ Young children may require lower doses (~0.6 mg/kg/hour) to achieve a desired antihypertensive effect. ▪ Bronchospasm has been reported infrequently in pediatric patients.
Nicardipine	Calcium channel antagonist (selective for arterial Ca^{2+} channels)	0.2–0.5 mcg/kg/min	3 mcg/kg/minute	Flushing Headache Reflex tachycardia	Renal Potential reduction needed in hepatic impairment	▪ Selective for arterial Ca^{2+} channels with minimal activity on myocardium ▪ Doses higher than 3 mcg/kg/minute have been reported with lack of additional benefit in BP reduction.
Sodium Nitroprusside	Direct vasodilator (venules and arterioles)	0.3–1 mcg/kg/minute	10 mcg/kg/minute	Cyanide toxicity Tachyphylaxis Thiocyanate toxicity	Renal Hepatic	▪ The typical maximal dose is 4 mcg/kg/minute, although doses as high as 10 mcg/kg/minute have been reported. ▪ May administer sodium thiosulfate to prevent or treat cyanide toxicity ▪ Tachyphylaxis may develop after prolonged treatment.

[a]Information from References 10, 37, 62, 66, 86, 91, 95, 97, 98, 103–105, 120–152, 154–161.
[b]All agents may cause hypotension.
B = bolus; BP = blood pressure; C = continuous infusion; IM = intramuscularly; IV = intravenously; Max = maximum; RAAS = renin-angiotensin-aldosterone system.

Clinical literature indicates that patients who receive a continuous infusion of 2 mcg/kg/minute or greater for at least 24 hours or those with renal or hepatic dysfunction are at increased risk; however, present evidence has failed to establish reference ranges for cyanide concentrations that correlate to toxicity in pediatric patients (References 123, 125–130). Focused on combating SNP-induced cyanide toxicity, some institutions add sodium thiosulfate to nitroprusside infusions to take advantage of its ability to reduce serum cyanide concentrations by replacing exhausted thiosulfate reserves (References 131–133). Of note, clinical literature describing the safety and efficacy of the prolonged coadministration of the two drugs is lacking.

Nicardipine

Mechanism/Use

Nicardipine is an intravenous CCB that has recently been studied with more frequency compared with other agents used for hypertensive emergencies in pediatric patients (References 134–141). Like SNP, it is considered a first-line treatment option for pediatric hypertensive crises (Reference 10). Its mechanism of action involves peripheral arterial vasodilation with minimal effects on the myocardium (Reference 10). Its relatively high affinity for vascular calcium channels and lack of activity on myocardial calcium channels causes SVR reduction with a potential to produce reflex tachycardia (References 134–136).

Pediatric Pharmacokinetics

Much like SNP, nicardipine has a pharmacokinetic profile that includes a rapid onset of action (1–2 minutes) and can be rapidly titrated (Reference 135). Drug elimination is highly driven by hepatic metabolism through cytochrome P450 (CYP) enzymes. Although a smaller percentage of the drug is excreted in urine and feces, no adjustments for renal dysfunction are required. Unlike SNP, its metabolism does not produce toxic metabolites, so it can safely be infused for a prolonged period (e.g., greater than 10 days) without risks of toxicity (Reference 135).

Labetalol

Mechanism/Use

Labetalol is yet another agent with limited pediatric data that is considered a first-line antihypertensive agent for pediatric hypertensive emergencies and urgencies (References 91, 120). Unlike nicardipine and nitroprusside, intravenous labetalol reduces BP without causing reflex tachycardia. This is because of its mechanism of antagonizing both α_1- and β-adrenergic receptors in a 1:7 ratio (Reference 142).

Pediatric Pharmacokinetics

Labetolol's onset of action occurs after only 5 minutes, and it can be titrated every 10 minutes (Reference 103). Compared with other continuously infused agents for pediatric hypertensive crisis, labetalol has a relatively long half-life of around 5.5–8 hours (Reference 142). Labetalol is hepatically metabolized by glucuronidation pathways and is unaffected by renal insufficiency (References 142–144).

Esmolol

Mechanism/Use

As previously stated, esmolol is a cardioselective β_1-adrenergic antagonist. Although esmolol may be used in hypertensive emergencies, most pediatric data are specific to use in children with supraventricular tachycardia and hypertension control after repair of aortic coarctation (References 145–151).

Pediatric Pharmacokinetics

One of the properties that makes esmolol an attractive agent for this indication is its immediate onset of action (less than 1 minute) and unique drug metabolism by red blood cell esterases, resulting in a half-life of 3–9 minutes in pediatric patients (References 145–147, 149–152). Neonates and infants have been reported to metabolize esmolol more rapidly than older children, adolescents, and adults; however, data are conflicting, with a reported maximum half-life difference of about 6 minutes, which is most likely clinically insignificant (References 145–147, 150–152).

Hydralazine

Mechanism/Use

Although hydralazine can be used in the treatment of pediatric hypertension, its primary utility resides in the treatment of acute hypertension and hypertensive emergencies (References 37, 91). A direct vasodilator, hydralazine causes a reduction in SVR by inhibiting calcium-dependent ATPase (adenosine triphosphate) and phosphorylation in arteriolar smooth muscle (References 92, 93, 122, 153). Recent reports describe the mechanism in more detail as stimulation of the HIE (hypoxia-inducible factor)-1-alpha protein by inhibiting PHD (prolyl hydroxylase domain) enzymes. This mechanism results in the induction of VEGF (vascular endothelial growth factor), endothelin-1, adrenomedullin, and heme oxygenase 1, all of which cause the intracellular accumulation of cGMP (cyclic guanosine monophosphate). This results in the clinical response of smooth muscle relaxation and arteriolar vasodilation (Reference 153).

Pediatric Pharmacokinetics

Typical onset of action for hydralazine occurs between 20 and 40 minutes after an oral dose (not as useful in hypertensive emergencies) and between 5 and 20 minutes after intravenous/intramuscular dosing (Reference 154). Not much is known about the specific pediatric pharmacokinetics of hydralazine aside from methods of drug elimination and onset of action. Hydralazine is highly removed from the body through the first-pass effect. It is mainly metabolized by acetylation in the liver and partly eliminated by the kidneys (References 10, 91, 122). Patients with severe renal dysfunction may exhibit a longer hydralazine half-life and may require less frequent dosing, depending on their underlying hepatic metabolism rate.

Clonidine

Mechanism/Use

Oral central α-agonists such as clonidine are also used to treat hypertensive urgencies. Their main effects cause vasodilation through α_2-stimulation and a subsequent reduction in sympathetic tone, which leads to a reduction in SVR and BP.

Pediatric Pharmacokinetics

With its rapid onset of action (15–30 minutes after oral ingestion), clonidine is an ideal oral agent for urgent treatment (Reference 86). Clinicians should exercise caution when using it for this indication because its 6- to 8-hour half-life (in adults) could result in a prolonged, dangerous decline in BP (References 86, 105). The pediatric pharmacokinetics and pharmacodynamics of orally administered clonidine are poorly understood. Rectal and nasal administration of clonidine in infants and children for anesthetic purposes have shown a half-life of 5–20 hours, possibly indicating prolonged activity in young children (References 156, 157).

Oral Calcium Channel Antagonists

Mechanism/Use

Oral calcium channel antagonists show differences in specificity for cardiac myocytes and vascular smooth muscle. The use of non-dihydropyridine CCBs (verapamil and diltiazem) has been reported in pediatric patients (Reference 62). The 4th Report does not include non-dihydropyridines or nifedipine as desirable agents for use in hypertensive crisis (Reference 10). Verapamil and diltiazem use is limited because of their negative inotropic and chronotropic activity through blockade of cardiac electrical conduction. The use of short-acting nifedipine, which has been well documented, is controversial (References 62, 97, 98, 158–160). Many authors do not recommend its use because of its overtly potent antihypertensive effects, which may cause significant morbidity and mortality related to a rapid and dangerous decline in BP (References 62, 97, 98, 158–160).

Unlike diltiazem and verapamil, dihydropyridines (excluding nifedipine) such as isradipine are more commonly used in children for hypertensive urgencies. Without disturbing myocardial electrical conduction, isradipine produces vasodilation and decreases SVR by exhibiting its primary actions on L-type calcium channels (Reference 158). Pediatric data are available on the use of isradipine for the treatment of acute hypertension; however, information on its use for hypertensive crisis in children is limited (References 106–109).

Pediatric Pharmacokinetics

Like those of other oral agents used for hypertensive urgencies, isradipine's pharmacokinetic profile includes a rapid onset of action (30–60 minutes), with peak effects occurring after 2–3 hours (Reference 91). It is metabolized by hepatic enzymes CYP3A3 and CYP3A4 with a half-life of about 3–8 hours (Reference 108). Because amlodipine does not have a rapid onset of action but has a long half-life, it is not used in hypertensive emergencies because of the inability to rapidly titrate its effects on hemodynamics.

Minoxidil

Mechanism/Use

Minoxidil is a direct arteriolar vasodilator, thus making it a potentially useful agent in the treatment of hypertensive urgencies and emergencies (References 91, 95). Its use, however, is usually reserved as a single dose to control hypertension while continuous-infusion agents are being prepared or when hypertension is resistant to several drug therapies (Reference 10).

Pediatric Pharmacokinetics

Peak drug activity occurs within 60 minutes of ingestion, and a half-life of 4 hours ensures rapid drug clearance (Reference 161). Drug elimination primarily occurs through hepatic glucuronidation with secondary renal elimination.

Monitoring Therapeutic Outcomes

Because hypertensive emergencies have a high propensity to cause marked acute morbidity and mortality, hypertensive emergencies should be monitored very closely in an institutional setting (e.g., in an intensive care unit), whereas the treatment of less severe forms of hypertension can be followed in an outpatient setting. When patients with hypertension are discharged

from the hospital, close follow-up should be scheduled to ensure continued adequate BP control, treatment of any underlying disease states, and limitation of adverse drug effects (Table 2) (Reference 10).

Conclusions

Although pediatric hypertension and hypertensive crises are relatively rare compared with the incidence in adults, they are both important public health concerns because of their ever-increasing incidence as well as their potential to cause damaging effects on the human body. Knowledge of pediatric hypertension guidelines, potential lifestyle modifications, and pediatric pharmacology of antihypertensive agents is essential to providing high-quality care that is safe and effective for pediatric patients.

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CHAPTER 12

Neonatal Respiratory Distress Syndrome and Bronchopulmonary Dysplasia

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Learning Objectives

1. Explain the pathophysiology and clinical presentation of respiratory distress syndrome (RDS) and bronchopulmonary dysplasia (BPD).
2. Identify nonpharmacologic approaches to the prevention and treatment of RDS and BPD.
3. Discuss the pharmacologic agents for the prevention and treatment of RDS and BPD.
4. Evaluate the risks and benefits of treatment modalities aimed at improving the clinical symptoms of infants with RDS and BPD.

Abbreviations in This Chapter

BPD	Bronchopulmonary dysplasia
FIO_2	Fraction of inspired oxygen
iNO	Inhaled nitric oxide
RDS	Respiratory distress syndrome

Introduction

Premature newborns commonly have complications with respiratory development and function. Respiratory distress syndrome (RDS) is a respiratory disorder caused by surfactant deficiency. Pulmonary surfactant prevents alveolar collapse to facilitate optimal gas exchange and prevent respiratory failure. Infants with RDS have lung immaturity that often requires oxygen supplementation and mechanical ventilation, both of which are risk factors for the development of bronchopulmonary dysplasia (BPD), a chronic lung disease of infancy in which the infant lung is characterized by inflammation and fibrosis. Recent treatment options and supportive therapies for RDS and BPD have significantly improved neonatal outcomes and survival.

Respiratory Distress Syndrome

Respiratory distress syndrome, historically known as hyaline membrane disease, is a lung condition of prematurity. It was a common cause of neonatal morbidity and mortality before the discovery of exogenous pulmonary surfactant several decades ago. Because RDS is considered a developmental disorder, the risk of RDS increases dramatically with decreasing gestational age and birth weight. Maternal steroid use before delivery promotes the maturation of the neonatal surfactant system to decrease the severity and incidence of RDS by 40% to 50% (Reference 1). Even with antenatal interventions, about 50% of infants born before 30 weeks' gestational age and 25% of infants born after 30 weeks' gestational age will develop RDS (Reference 2). Furthermore, surfactant therapy has significantly reduced the incidence of death and BPD in premature infants with RDS.

Pathophysiology

Surfactant acts to lower surface tension at the air-liquid interface in the alveoli to prevent alveolar collapse. A sufficient amount of surfactant to sustain normal lung function is not acquired until the end of the saccular phase (Figure 1) of lung development, which occurs around 36 weeks' gestational age (Reference 4). An inadequate production or impaired release of pulmonary surfactant because of prematurity will result in RDS at birth. For comparison, premature infants have one-tenth of the surfactant pool compared with term neonates (10 mg/kg vs. 100 mg/kg) (Reference 5). Consequently, inadequate surfactant production leads to atelectasis, a complete or partial collapse of the lung, and impaired gas exchange.

Surfactant consists of highly organized lipid and surfactant proteins in the following concentrations: saturated phosphatidylcholine (50%), unsaturated phosphatidylcholine (20%), natural lipids (8%), phosphatidylglycerol (8%), other phospholipids (6%), and surfactant proteins (8%) (Reference 5). Although each surfactant protein has a unique function (Table 1), the critical components required for normal respiratory function are phosphatidylcholine, surfactant protein B, and surfactant protein C. An immature lung has lower percentages of these components, hindering the premature infant from adequately lowering the surface tension to allow adequate gas exchange within the alveoli. The severity of RDS is dictated by the extent of lung injury as a result of progressive atelectasis and ventilation-perfusion mismatch. The pathogenesis of lung damage may be further complicated by a structurally immature lung, pulmonary edema, and impaired alveolar ventilation.

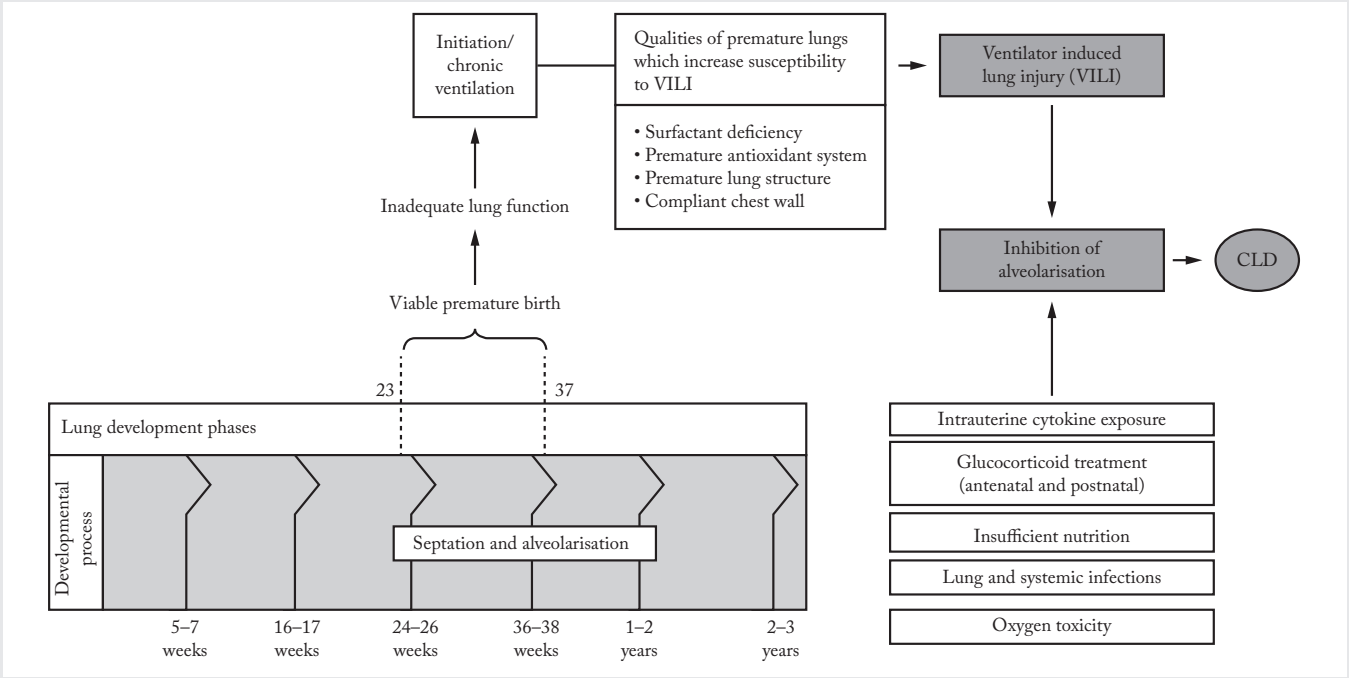


Figure 1. The pulmonary development phases and the impact of ventilator-induced lung injury and other factors that contribute to BPD or CLD.

BPD = bronchopulmonary dysplasia; CLD = chronic lung disease.
Reproduced from Donn SM, Sinha SK. Minimising ventilator induced lung injury in preterm infants. Arch Dis Child Fetal Neonatal Ed 2006;91:F226–F230 (Reference 3) with permission.

Clinical Presentation

Neonates with RDS usually present soon after birth with signs of respiratory distress such as tachypnea, grunting, retractions, and cyanosis (Reference 6). Physical findings may include the use of accessory breathing muscles, nasal flaring, tachycardia, and increasing oxygen requirements. A characteristic chest radiograph shows diffuse reticular-granular opacification with defined large airways. Other neonatal disorders that could present similarly to RDS include early-onset sepsis, transient tachypnea of the newborn, and spontaneous pneumothorax (Reference 6). The diagnosis of RDS is based on the infant's clinical presentation at birth and supported by findings on the chest radiograph consistent with surfactant deficiency. Infants who are younger than 30 weeks' gestational age or who did not receive antenatal steroids have the highest risk of RDS.

The clinical course is dictated by the severity of RDS, birth weight, gestational age, and extent of lung injury. In uncomplicated cases, RDS is transient, and recovery is expected within several days. However, RDS may be complicated by other common neonatal comorbidities (e.g., patent ductus arteriosus, infection). The infant may require supplemental oxygen or prolonged mechanical ventilation, resulting in extensive lung injury with eventual progression to BPD.

Treatment

Therapeutic Goals

The goal of RDS treatment is aimed at rapidly replacing pulmonary surfactant and minimizing the pathologic sequelae of acute pulmonary injury. The initial management of RDS immediately after birth includes early surfactant administration and establishment of adequate ventilation and oxygenation. The desired outcome is limiting the severity of lung injury and reducing the duration of supplemental oxygen or mechanical ventilation with continued efforts to prevent the development of BPD.

Nonpharmacologic Therapy

It is critical to establish ventilation and oxygenation promptly after birth to prevent pulmonary vasoconstriction and subsequent atelectasis. Infants usually require supplemental oxygen, continuous positive airway pressure, or mechanical ventilation at any time during the clinical course of RDS. In general, continuous positive airway pressure is adequate for mild or moderate RDS and may reduce the need for additional surfactant doses. Supplemental oxygen or mechanical ventilation should be discontinued as soon as tolerated to minimize the risk of BPD.

Table 1. Functions of Surfactant Proteins

Surfactant Proteins	Function
A	Hydrophilic protein that regulates the turnover of pulmonary surfactant, formation of tubular myelin, and immunity
B	Hydrophobic protein that is involved in the formation of tubular myelin and that facilitates improvement in surfactant surface activity
C	Improves spreadability and surfactant surface activity
D	Involved in bacterial opsonization

Pharmacologic Therapy

Surfactant Replacement Therapy

Surfactant therapy is the standard of care for the prophylaxis and treatment of RDS. Systematic reviews have confirmed the many benefits of surfactant replacement, which include decreased ventilation requirements and a reduced incidence in mortality, pneumothorax, and pulmonary interstitial emphysema. Infants younger than 30 weeks' gestational age or with a birth weight of less than 1250 g have the greatest reduction in mortality rates with surfactant therapy (Reference 7). However, the occurrence of other neonatal comorbidities (e.g., intraventricular hemorrhage, necrotizing enterocolitis, nosocomial infections, retinopathy of prematurity, and patent ductus arteriosus) has not changed with the introduction of surfactant (References 6, 8, 9).

Types of Surfactant

The two types of exogenous surfactants are synthetic and natural. Synthetic surfactants contain phospholipids without surfactant proteins and are currently not approved for use in the United States (Reference 2). Natural, also known as animal-derived, surfactants are modified or purified from bovine or porcine lungs. Systematic reviews show better clinical outcomes and improved survival with animal-derived compared with synthetic surfactants in the prophylaxis and treatment of RDS (References 2, 10).

Infants receiving animal-derived surfactant have shown significant reductions in ventilator requirement and the incidence of pneumothoraces and mortality, with only marginal increases in low-grade intraventricular hemorrhage (Reference 10). Adverse immunologic or infectious complications with natural surfactant have not been recognized. Animal-derived surfactant is considered the mainstay treatment of RDS in clinical practice (Reference 10).

Beractant, calfactant, and poractant alfa are the commercially available animal-derived surfactants in the United States. These products have varying amounts of phospholipids and surfactant proteins B and C. They also differ in viscosity and administration volume (Table 2). All commercially available natural surfactant products are effective for the prevention and treatment of RDS. There are no randomized controlled trials to support the superiority of one preparation over the other (References 2, 11). However, treatment with poractant alfa allowed for a quicker weaning of oxygen and ventilatory pressures (References 11). Additionally, a recent meta-analysis showed a significant decrease in mortality with high-dose poractant alfa (200 mg/kg/dose) compared with beractant (100 mg/kg/dose), with the poractant alfa group also requiring fewer total doses (Reference 12).

Mechanism of Action

Exogenous surfactant replaces deficient or dysfunctional pulmonary surfactant in infants with RDS or premature infants at risk of developing RDS. Surfactant deficiency increases surface tension at the air and alveolar surfaces leading to alveolar collapse. Because of unopposed

Table 2. A Comparison of the Source, Composition, and Dose of Animal-Derived Surfactants Available in the United States

Surfactant	Animal Source	Phospholipid Concentration (mg of phospholipids/kg)	Initial Dose (mg of phospholipids/kg)	Subsequent Doses (mg of phospholipids/kg)	Dosing Interval (hours)	Maximum Total Doses
Beractant	Bovine	25	100 mg/kg (4 mL/kg)	100 mg/kg (4 mL/kg)	6	4
Calfactant	Bovine	35	105 mg/kg (3 mL/kg)	105 mg/kg (3 mL/kg)	12	4
Poractant alfa	Porcine	80	200 mg/kg (2.5 mL/kg)	100 mg/kg (1.25 mL/kg)	12	3

surface tension forces, an increase in the work of breathing is required to reinflate the alveoli (Reference 13). Surfactant acts to lower the surface tension at the air-liquid interface to stabilize the alveoli. Once surfactant is instilled and evenly distributed to the distal lung, an acute response occurs within minutes. The exogenous surfactant will decrease the surface tension to allow the lung to inflate at a lower pressure and a greater volume, resulting in a rapid oxygenation response. The result is a reduction in the work of breathing, an increase in lung compliance, the resolution of RDS symptoms, and a subsequent reduction in lung injury.

Prophylaxis and Rescue Therapy

Prophylactic surfactant therapy is surfactant administration within 30 minutes of birth to neonates at high risk of having RDS before the diagnosis of RDS is confirmed. Meanwhile, rescue surfactant therapy is administered to neonates with established RDS within 12 hours of birth. Early rescue therapy is surfactant administration within 1–2 hours of birth, whereas late rescue therapy is administration after 2 hours (Reference 14).

Prophylactic surfactant replacement has the advantage of replacing surfactant before the onset of respiratory symptoms and lung injury. Prophylaxis in premature neonates improves significant clinical outcomes such as death, pneumothorax, and pulmonary interstitial emphysema (Reference 15). However, the impact of prophylactic surfactant administration on the risk of BPD is unclear (Reference 14). A prophylactic approach should be considered in neonates who are at extremely high risk of RDS, such as those who were born at or earlier than 30 weeks' gestation or who were not exposed to antenatal steroids (Reference 14). Although these infants will also benefit from rescue surfactant therapy, the prophylactic approach decreases the severity and complications of RDS (Reference 14). Possible clinical risks of a prophylactic approach are unnecessary drug exposure and intubation in infants with respiratory disorders other than RDS (e.g., pulmonary hypoplasia, lung injury).

Few studies have compared prophylactic surfactant therapy with early or late rescue therapy. The limited data show better outcomes with prophylactic administration, but these therapies were mostly studied in infants who were not exposed to antenatal steroids (Reference 14). Surfactant replacement, either prophylactic or rescue, should occur before or soon after the presentation of RDS to optimize the clinical benefits of drug therapy.

Repeated Surfactant Doses

Surfactant doses may be repeated up to the recommended maximum number of treatments determined by the surfactant product (Table 2) if persistent respiratory distress is observed 6–12 hours after the initial dose. Infants with lung injury from mechanical ventilation or supplemental oxygen are most likely to benefit from more than a single dose of surfactant because pulmonary edema or inflammation will inhibit surfactant function (Reference 5). A second dose of surfactant may be necessary if the infant continues to need mechanical ventilation with an oxygen requirement (FIO_2 [fraction of inspired oxygen]) of greater than 30% or 40% (Reference 16).

Several studies have shown better outcomes with multiple doses as opposed to a single dose of surfactant in premature infants with RDS (References 7, 17). A meta-analysis of two trials comparing single versus several doses of surfactant showed a reduction in the incidence of pneumothorax with a trend toward decreased mortality when more than one dose of surfactant was administered (Reference 17). No complications from multiple surfactant doses were observed in these trials. There is a paucity of data distinguishing the differences in the outcomes of two doses compared with three or four doses of surfactant. Criteria for multiple dosing of surfactant need to be further defined to limit unnecessary treatment. The infant should be evaluated after each surfactant administration for signs of clinical improvement, as evidenced by a reduction in oxygen requirement or ventilator support. In general, repeated doses are not indicated if the infant had a favorable improvement in oxygenation and has no significant respiratory distress.

Administration

Surfactant is administered by instilling the solution through a catheter into the endotracheal tube. The volume of medication and number of aliquots depend on the specific surfactant product (Table 1). The neonate may be placed in several positions to facilitate surfactant distribution, which varies according to the manufacturer's guideline for the individual products. For example, each dose of beractant is administered in four 1-mL/kg aliquots with the infant in four different positions: (1) inclined slightly downward with the head turned right, (2) inclined slightly downward with the head turned left, (3) inclined slightly upward with the head turned right, and (4) inclined slightly upward with the head turned left. This administration technique ensures a uniform and rapid distribution of surfactant in the lungs. Complications can occur with transient airway obstruction or inappropriate instillation into the right mainstem bronchus or esophagus, so administration should be performed with the guidance of a trained clinical expert (e.g., respiratory therapist).

Monitoring Parameters and Adverse Effects

Improvements in lung volume and compliance occur rapidly after surfactant administration. Close observation is critical because the infant may require prompt

mechanical ventilation changes to prevent further lung injury and pneumothorax. Although considered a well-tolerated therapy, surfactant may cause adverse effects such as apnea, bradycardia, and oxygen desaturation. An infrequent complication of surfactant therapy is pulmonary hemorrhage with extremely low-birth-weight infants at the highest risk (References 14, 17). Future research should focus on optimizing surfactant preparations, minimizing acute lung injury, and exploring noninvasive administration techniques to reduce short- and long-term complications of RDS, such as the development of BPD.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia is often the pulmonary sequelae of RDS and the most common cause of morbidity in surviving premature infants in the United States (References 18–21). Also referred to as chronic lung disease of infancy, BPD begins with any neonatal disorder that causes postnatal respiratory failure requiring long-term mechanical ventilatory or supplemental oxygen support. Both the underlying condition and the treatment interventions for neonatal respiratory failure contribute to airway inflammation, leading to chronic airflow obstruction and hyperreactivity in the infant with BPD (Reference 22). Infants younger than 30 weeks' gestational age or weighing less than 1500 g have the highest risk of BPD. Of the infants born under 1500 g—about 1.5% of all newborns in the United States—20% will develop BPD (Reference 23).

Pathophysiology

The premature lung is most susceptible to lung injury during the saccular stage of lung development between 24 and 36 weeks' gestation. At this stage, lung structure and function are immature, increasing the likelihood of lung injury and disruption of alveolarization (Reference 24). Mechanical ventilation is the primary cause of acute lung injury because of an overdistention of the immature airspaces. This cellular and interstitial lung injury triggers the release of proinflammatory cytokines, resulting in increased alveolar permeability and leakage of protein and water. In addition, high concentrations of oxygen produce free radicals and subsequent damage to the lung parenchyma in the underdeveloped respiratory epithelium and antioxidant defense system (Reference 25). Airway hyperactivity, smooth muscle hypertrophy, and bronchoconstriction are characteristic of the acute stage of BPD. This period occurs during the first few weeks of life after early lung injury, generally around 28–36 weeks' postmenstrual age. The progression to chronic BPD, which occurs after 36 weeks' postmenstrual age, is marked by pulmonary fibrosis and muscularization, leading to a reduction in lung compliance and impairment of gas exchange (References 26, 27). Other factors that may contribute to the pathophysiology of BPD include infection, steroids, and surfactant deficiency (Figure 1). Unfortunately, there is very limited knowledge regarding the time to complete resolution of BPD, which may last several months to years (Reference 26).

Clinical Presentation

Infants with BPD often present with chronic respiratory signs such as tachypnea, shallow breathing, and retractions. Coarse rhonchi, diffuse rales, and wheezes are heard on auscultation. Chest radiograph often reveals diffuse haziness and lung hypoinflation (Reference 28). The severity of BPD is related to the degree of injury to the airways and distal lung. Infants with moderate to severe BPD may have acute episodes of pulmonary decompensation, bronchoconstriction, or reversible bronchospasm triggered by worsening pulmonary function. Acute exacerbations are described as a combination of an increased work of breathing or oxygen requirement and the presence of apnea or bradycardia. These episodes may be related to infections, severe airway reactivity, increased pulmonary edema, or the development of tracheobronchomalacia. Bronchopulmonary dysplasia may be accompanied by cardiovascular abnormalities (e.g., cardiomegaly), emphysema, pulmonary fibrosis, or lung hyperexpansion (Reference 1). Although BPD is primarily a respiratory disease, short- and long-term complications could involve many systems, including pulmonary hypertension, cardiac dysfunction (e.g., cor pulmonale), poor neurodevelopment, and poor growth in severe cases (Reference 29).

A diagnosis of BPD is made if the infant continues to require supplemental oxygen or respiratory support at 28 days of life and/or 36 weeks' postmenstrual age (Reference 1). The National Institute of Child Health and Human Development, the National Heart, Lung and Blood Institute, and the Office of Rare Diseases further categorize the disease into mild, moderate, or severe BPD on the basis of gestational age (younger than 32 weeks or 32 weeks or older), oxygen requirement (FIO_2 of less than 30% or FIO_2 of 30% or greater), or need for positive-pressure ventilation (Reference 30). The greatest risk factors for BPD are prematurity, chronic exposure to mechanical ventilation, and prolonged oxygen supplementation (Reference 31).

Treatment

Therapeutic Goals

Infants often present in acute exacerbation with tachypnea, retractions, or wheezing. The therapeutic goal is an overall improvement in clinical symptoms by

minimizing further lung injury and complications, decreasing oxygen requirements, and achieving optimal nutrition for adequate lung growth.

Nonpharmacologic Therapy

Mechanical Ventilation and Supplemental Oxygen

Infants with severe BPD often require prolonged ventilator support. Although mechanical ventilation contributes greatly to lung injury, the infant may require respiratory support in the acute phase of BPD during the first several weeks after preterm birth (Reference 32). Ventilator adjustments should be made accordingly to avoid hyperventilation while maintaining appropriate oxygen saturations and adequate gas exchange (Reference 33).

Continuous positive airway pressure ventilation is the preferred ventilatory support technique because it does not require intubation and mechanical ventilation (Reference 34). Infants can be weaned off continuous positive airway pressure to supplemental oxygen alone as pulmonary function improves. In the chronic phase and more severe form of BPD, weaning ventilator settings is usually not possible until the infant shows good growth and a steady weight gain. If the infant can maintain oxygen saturations above 90% during periods of sleep, feedings, and activity, a trial off supplemental oxygen can be considered. Eventually, adequate oxygenation can be maintained with room air as BPD improves or resolves.

Fluid Restriction

Pulmonary edema decreases lung compliance and increases the need for mechanical ventilatory support. High fluid intake or inadequate urine output places the premature infant at a greater risk of pulmonary edema (Reference 35). Restricting fluid volume from medications or nutrition could help counteract the pulmonary lung injury and capillary leak seen in BPD. In a randomized study of infants weighing less than 1751 g, the investigators compared the control group having a fluid intake of 200 mL/kg/day with a restricted group having a fluid intake of 150 mL/kg/day after the first week of life. A significant difference in mortality and BPD, defined by imaging findings, clinical symptoms, and oxygen requirement at 1 month of life, was observed with the group receiving fluid at 150 mL/kg/day (Reference 36). One argument is that the study was quite liberal with the fluid restriction because 150 mL/kg/day could be considered the standard maintenance fluid intake, not a restricted amount in neonates (Reference 1). Although it is uncertain whether fluid restriction less than 150 mL/kg/day provides additional benefit, fluid intake should be kept at the minimum required for optimal growth and adequate urine output to avoid pulmonary edema (References 36, 37).

Pharmacologic Therapy

Most treatment modalities are aimed at improving the clinical symptoms of infants with BPD. Multidrug therapy typically includes diuretics, bronchodilators, and corticosteroids. However, the exact mechanism and safety of these drug therapies are not well studied and have not been shown to reverse pulmonary injury in the BPD population. Currently, there is no optimal agent or regimen for the prevention and treatment of BPD, and an evidence-based treatment guideline does not exist. In addition to the patient's disease severity, the risks of treatment and potential adverse events must be considered before initiating pharmacologic therapy.

Diuretics

Diuretics are often used in infants with BPD to improve pulmonary function (Reference 38). They increase pulmonary compliance by decreasing pulmonary resistance and interstitial lung fluid (Reference 1). A transient improvement in gas exchange and reduction in oxygen requirement are observed when diuretics are administered to an infant with BPD (Reference 38). Diuretics are usually considered when the infant with BPD cannot be weaned off aggressive respiratory support or has cardiac failure (Reference 23). They are also useful when fluid restriction causes nutritional compromise and inadequate delivery of calories to promote lung growth. The common classes of diuretics used in BPD are loop and thiazide diuretics (Reference 39).

The loop diuretic used most frequently in neonates is furosemide, a potent diuretic that acts in the ascending loop of Henle and distal tubule (Reference 40). Around 25% of the filtered sodium is reabsorbed to cause significant diuresis (Figure 2). Furosemide is thought to be effective in BPD by increasing plasma oncotic pressure and lymphatic flow while decreasing interstitial edema and pulmonary vascular resistance. A single dose of intravenous furosemide (1 mg/kg/dose) acutely improved pulmonary mechanics compared with placebo in a study of 10 infants with chronic BPD who were not dependent on oxygen. Airway resistance was significantly decreased 1 hour after the furosemide dose. However, this effect returned to baseline values after 2 hours (Reference 42). Age appears to be a contributing factor in the beneficial response of furosemide in infants with BPD. In a systematic study of premature infants with, or developing, BPD who received intravenous or oral furosemide, no benefits were detectable in infants younger than 3 weeks. However, in infants older than 3 weeks, the acute and chronic administration of furosemide improved lung compliance, airway resistance, and oxygenation for at least 1 hour after the furosemide dose (Reference 43). Although short-term improvements in

pulmonary mechanics have been observed, there is no current evidence that furosemide improves clinically significant outcomes such as mortality or decreases the incidence of BPD (Reference 38).

Chronic therapy with a loop diuretic may present several complications, including electrolyte disturbances, osteopenia, and ototoxicity (Reference 1). Hypokalemia, hyponatremia, and contractional metabolic alkalosis are often observed in clinical practice, and supplementation with potassium chloride is usually required. Furosemide also increases urinary calcium excretion, which could lead to nephrocalcinosis and nephrolithiasis in infants (Reference 44). Although rare, ototoxicity and transient deafness are possible when furosemide is used chronically or in conjunction with other ototoxic medications such as aminoglycosides. Inhaled furosemide has been studied in BPD as a result of complications seen with systemic diuretics. Because of the limited body of evidence and conflicting results related to pertinent clinical outcomes, the routine use of inhaled furosemide in infants with BPD is not recommended (References 45, 46).

Thiazide diuretics act in the distal convoluted tubule, where active reabsorption of only 4% to 8% of filtered sodium, chloride, and calcium occurs. Thiazide diuretics also improve pulmonary mechanics in premature infants with BPD who are older than 3 weeks (Reference 47). The two most extensively studied thiazide diuretics in neonates are chlorothiazide and hydrochlorothiazide. These agents are useful in the pharmacologic armamentarium for infants experiencing complications or tolerance of furosemide. Electrolyte abnormalities may be observed but to a considerably lesser degree than with furosemide therapy. Nephrocalcinosis is usually not seen because less calcium resorption occurs with a thiazide than with a loop diuretic (Reference 38). Although less potent and modestly effective compared with furosemide, hydrochlorothiazide or chlorothiazide may be a better alternative for the chronic management of BPD because of its more favorable adverse effect profile (References 38, 40).

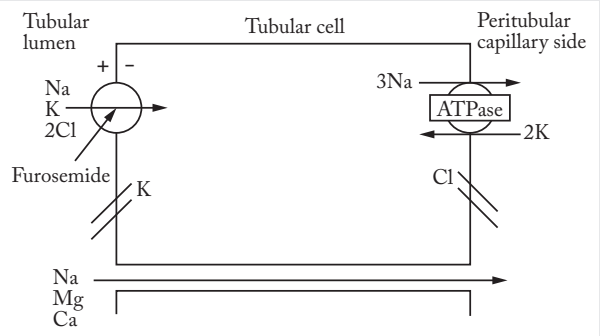


Figure 2. Furosemide binds to the chloride site of the sodium/potassium/chloride cotransporter in the tubule lumen to cause increased excretion of water, sodium, chloride, magnesium, and calcium.

Reproduced from Moghal NE, Shenoy M. Furosemide and acute kidney injury in neonates. Arch Dis Child Fetal Neonatal Ed 2008;93:F313–F316 (Reference 41) with permission.

Loop diuretics are most beneficial in the acute BPD phase, and thiazide diuretics are often used in ventilator-dependent infants with chronic BPD when fluid restriction is ineffective. However, whether the chronic use of diuretics improves important clinical outcomes remains to be seen (Reference 38). The duration of diuretic therapy depends on individual responses to diuretics and improvement in symptoms during acute exacerbations. Close monitoring of electrolyte abnormalities is important, and appropriate electrolyte supplementation is required during diuretic therapy.

Inhaled Bronchodilators

Bronchodilators act to dilate the small airways caused by muscle hypertrophy observed in infants with moderate or severe BPD (References 22, 48). They improve airway hyperactivity that causes flow limitation and obstruction through narrowing of the bronchi and may be effective as an adjunctive therapy for the treatment of acute exacerbations to obtain a short-term resolution of symptoms. Two classes of inhaled bronchodilators used in BPD are β-agonists and anticholinergic agents (Reference 1). However, the use of bronchodilators has not been well studied, and their impact on the course of BPD has not been elucidated (Reference 1).

β-agonists acutely improve pulmonary resistance and lung compliance through bronchial smooth muscle relaxation. Unfortunately, these effects are short term, with a return to baseline 4 hours after drug administration. In a double-blind, placebo-controlled study of 173 ventilator-dependent infants younger than 31 weeks' gestation, albuterol did not show any difference in important outcomes such as mortality, chronic lung disease, or duration of ventilator support (Reference 49). Adverse effects of inhaled β-agonists include hypokalemia, tachycardia, hypertension, and arrhythmias.

Inhaled anticholinergic agents such as atropine and ipratropium block the action of acetylcholine in bronchial smooth muscle, resulting in bronchodilation. Adverse effects of inhaled anticholinergic agents are dyspnea, palpitations, dyspepsia, and upper respiratory tract infections. Ipratropium is a more potent bronchodilator than atropine with a more favorable adverse effect profile (Reference 50). Although rarely used in clinical practice, an inhaled anticholinergic may be a

therapeutic option in addition to β-agonist therapy to improve symptomatic and reversible airway obstruction. Synergy occurs by interfering with vagal-mediated bronchoconstriction (Reference 48).

In the chronic stage, lung pathology becomes fibrotic and less sensitive to the effects of inhaled therapy; thus, a positive response to inhaled bronchodilators may not be observed in all infants (Reference 48). To ensure optimal drug therapy, a spacer and mask should be used when delivering bronchodilators through a metered dose inhaler. Routine or chronic use of inhaled bronchodilators is not recommended but may be considered if short-term clinical improvements (e.g., resolution of airway obstruction) are observed. The long-term efficacy of bronchodilators in BPD has not been studied, and their effects on lung development, prevention of exacerbations, and improvement of the quality of life remain to be seen (Reference 23).

Corticosteroids

Airway inflammation in BPD suggests a beneficial role for systemic and inhaled corticosteroids. Corticosteroids decrease inflammation by suppressing neutrophil migration and production of inflammatory mediators. Their use in neonatal lung disease was first reported in the 1950s, and in the 1980s and 1990s they became commonly used in practice (Reference 51). The decision to use corticosteroids to treat BPD remains controversial because of their high risk potential and long-term consequences.

Dexamethasone is the first well-studied corticosteroid in the management of BPD for its potent anti-inflammatory properties. Short-term treatment with dexamethasone reduces the need for supplemental oxygen, with no difference in mortality before hospital discharge (Reference 48). A higher incidence of growth failure, hyperglycemia, hypertension, and hypertrophic cardiomyopathy was noted in the infants treated with dexamethasone. Follow-up data in the late 1990s showed an increased risk of neurodevelopmental consequences. Infants who received a 4-week course of dexamethasone within 12 hours of birth had twice the risk of cerebral palsy compared with the control group (Reference 52). In systematic reviews, the most common dexamethasone dosing regimen was 0.5 mg/kg/day divided in two doses for 3 days, followed by 0.25 mg/kg/day for 3 days, 0.12 mg/kg/day for 3 days, and 0.05 mg/kg/day for 3 days. These were discovered to be relatively high-potency doses of corticosteroid and may have contributed to the harmful neurodevelopmental outcomes (References 53–55). The use of dexamethasone for BPD is no longer recommended because of the significant risk of long-term neurodevelopmental sequelae.

Data on the adverse effects of dexamethasone have led to studies with other corticosteroids, specifically hydrocortisone, for the treatment and prevention of BPD. In a retrospective study evaluating the short- and long-term outcomes of hydrocortisone- and dexamethasone-tapering regimens, both corticosteroids showed effectiveness in decreasing oxygen requirements. Follow-up at 5–7 years of age found that children treated with hydrocortisone needed less special school education and had better neurodevelopmental outcomes than those treated with dexamethasone (Reference 56). Although hydrocortisone appears to have a better adverse effect profile, its routine use for the prevention and treatment of BPD in preterm infants is not recommended by the American Academy of Pediatrics (Reference 57). Therapy may only be reasonable for ventilator-dependent infants with exceptional BPD on maximum support in which hydrocortisone may be lifesaving (Reference 1). Inhaled corticosteroids could improve short-term pulmonary exacerbations with minimal systemic absorption, but evidence is limited for their role in preventing and treating BPD (Reference 58).

BPD Prevention

The most effective means of preventing BPD is the prevention of prematurity, RDS, and subsequent lung injury. However, several pharmacologic therapies have been investigated to prevent BPD development (Table 3). These therapies remain largely controversial without many controlled studies, but they could be effective in combination with other preventive strategies. The clinician should outweigh the risks and benefits of each preventive modality.

Vitamin A

Vitamin A is essential for tissue differentiation and cell growth. Premature neonates with extremely low birth weights have inherently low plasma concentrations of vitamin A, possibly predisposing these infants to BPD. A multicenter, randomized trial evaluated the effectiveness of vitamin A supplementation in 807 infants with birth weights between 401 g and 1000 g who were ventilator- or oxygen-dependent at 24 hours of life (Reference 59). Vitamin A (5000 international units) was administered three times/week intramuscularly for 4 weeks. The vitamin A group had a significant reduction in mortality or BPD at 36 weeks of age (55% vs. 62%). Infants with birth weights less than 1000 g may benefit from vitamin A supplementation to decrease the risk of BPD.

Inhaled Nitric Oxide

Inhaled nitric oxide (iNO) may prevent BPD in premature patients at high risk of developing the disease by decreasing ventilation-perfusion mismatch, reducing inflammation, and restoring normal growth in

Table 3. Medications That Have Been Studied for BPD Prevention

	Vitamin A	Nitric Oxide	Caffeine Citrate
Administration route	Intramuscular	Inhalation	Oral, intravenous
Dosing	5000 international units three times/week	20 ppm for 2–3 days; then decrease to doses of 10, 5, and 2 ppm at weekly intervals	Loading dose: 20–25 mg/kg/dose; Maintenance dose: 5–10 mg/kg/day
Therapy duration	28 days	24 days	Until apnea of prematurity resolves
Adverse effects	Allergic reactions (rare)	Hypotension Rebound syndrome	Failure to gain weight Jitteriness Hyperreflexia Seizures

the premature lung. A multicenter, randomized study involving 793 premature newborns with respiratory failure requiring mechanical ventilation evaluated the effectiveness of low-dose iNO (5 ppm) or placebo for 21 days (Reference 60). There was no difference in the incidence of mortality or BPD between the two groups (71.6% vs. 75.3%). However, infants with a birth weight greater than 1000 g had a 50% reduction in the incidence of BPD; initiation of low-dose iNO may be beneficial in this weight group. Another randomized study of 294 premature neonates who received decreasing concentrations of iNO for a minimum of 24 days (starting dose of 20 ppm) showed a difference in survival rate without BPD (43.9% vs. 36.8%) when iNO was initiated between 7 and 21 days of age (Reference 61). The use of iNO for BPD prevention is not routinely recommended in clinical practice by the National Institutes of Health because of inconclusive evidence and overall cost of therapy.

Caffeine Citrate

Caffeine is a respiratory stimulant in premature neonates and is effective in the treatment of apnea of prematurity (see Apnea of Prematurity chapter). A large, international, randomized, placebo-controlled trial of caffeine citrate was conducted in 2006 infants with birth weights of 500–1250 g (Reference 62). Eligible patients received an intravenous loading dose of caffeine citrate of 20 mg/kg, followed by a maintenance dose of 5 mg/kg or normal saline. The daily maintenance dose was increased to a maximum of 10 mg/kg if apneic episodes persisted. Although BPD was not the primary outcome assessed, a significant reduction in BPD was observed in the caffeine group. Of the 963 infants in the caffeine group who survived at 36 weeks' postmenstrual age, significantly fewer infants in the caffeine group developed BPD compared with infants in the control group (36.3% vs. 46.9%). The investigators speculated that the reduced incidence in BPD was a result of the decreased duration of supplemental oxygen and positive-pressure ventilation observed in the caffeine group. Caffeine citrate should be routinely used in all premature infants at risk of severe apnea. It could prevent the need for invasive mechanical ventilation and progression of BPD.

Discharge Planning

Infants with BPD may be ready for discharge if their respiratory status is stable during periods of sleep, feeding, or activity without significant oxygen desaturation. Although supplemental oxygen is often discontinued before discharge from the neonatal intensive care unit, home oxygen therapy is available and may be offered with periodic assessment of oxygen saturation (Reference 27). Parents should learn about cardiopulmonary resuscitation techniques, signs of decompensation, equipment use, medication administration, and nutritional guidelines before discharge. Infants with BPD are at high risk of long-term pulmonary complications (Reference 62). They should receive routine vaccinations, including pneumococcal and influenza vaccines, and prophylaxis for respiratory syncytial virus with palivizumab (see Lower Respiratory Tract Infections chapter) (Reference 46).

Conclusions

The discovery of surfactant has significantly improved the morbidity and mortality of premature infants with RDS. Because of the improved survival of these infants, the rate of BPD has also increased (Reference 50). Although several strategies have been proposed to prevent and treat BPD, an evidence-based approach should be used when managing this vulnerable population. Future research should be aimed at identifying optimal treatment strategies to improve the long-term outcomes of premature infants with RDS and BPD.

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CHAPTER 13

Apnea of Prematurity

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Learning Objectives

1. Describe the clinical presentation and pathophysiology of apnea of prematurity (AOP).
2. Identify nonpharmacologic approaches to the treatment of AOP.
3. Discuss the pharmacologic agents for the treatment of AOP.
4. Evaluate the risks and benefits of treatment modalities aimed at improving the clinical symptoms of infants with AOP.

Abbreviations in This Chapter

AOP	Apnea of prematurity
CPAP	Continuous positive airway pressure
CYP	Cytochrome P450
V/Q	Ventilation Perfusion

Introduction

Apnea, a brief cessation of breathing lasting 5–10 seconds, is common in premature neonates as a manifestation of an immature respiratory control system (Reference 1). These episodes become pathologic when they are prolonged more than 20 seconds (Reference 2). Apnea of prematurity (AOP) is defined by the American Academy of Pediatrics as the "cessation of breathing for at least 20 seconds or as a briefer episode of apnea associated with bradycardia, cyanosis, or pallor" (Reference 3). Symptomatic neonates may have changes in hemodynamic, ventilation, and oxygenation parameters that are largely dependent on the duration of the apneic episodes (References 4–6). Apnea of prematurity has potentially life-threatening or severe neurodevelopmental consequences if left untreated (References 5, 7). Fortunately, nonpharmacologic and pharmacologic treatment strategies have made AOP a manageable condition of prematurity.

Epidemiology

The exact incidence of AOP is unknown because a standardized criterion for the diagnosis of symptomatic apnea is not currently available. However, apnea occurs more frequently in premature neonates than in term neonates (Reference 8). It is estimated that 70% of premature neonates with a birth weight less than 1500 g will have at least one clinically observed episode of symptomatic apnea while admitted in the neonatal intensive care unit. Around 20% of these neonates will have an identified etiology, and the other 80% will have a nonspecific medical cause of apnea (Reference 9). Because of maturational development, the resolution of apneic episodes typically occurs before 37 weeks' postmenstrual age in neonates born after 28 weeks' gestation. However, infants born before 28 weeks' gestation may have frequent and persistent apnea after 37 weeks' postmenstrual age (References 8, 10). After 43 weeks' postmenstrual age, severe apneic events are rare and do not occur any more frequently in premature infants than in healthy term infants (Reference 11).

Pathophysiology

Three main components are required for normal rhythmic breathing in the neonate: (1) central respiratory drive, (2) maintenance of airway patency, and (3) adequate respiratory muscle function. Consequently, apnea in premature neonates can be precipitated by an immature central respiratory drive, a dysfunctional upper airway, and underdeveloped respiratory muscles (References 12, 13). An immature brainstem is the primary reason for hypoventilation and cyanotic episodes in an apneic premature neonate (Reference 14). Central respiratory control involves a complex interaction of sensory stimulation from the medulla of the brain. The chemoreceptor stimuli are transmitted through the afferent pathways to regulate the respiratory system. In AOP, there is either an improper transmission of these signals or a lack of appropriate respiratory pump control (References 9, 15, 16).

Maintaining airway patency is challenging in neonates because of immature neuromuscular function and reflexes in the upper airway. This results in nasal and hypopharyngeal airway obstruction leading to apnea (References 17, 18). Overall weakness in the muscles involved in respiration (diaphragm and intercostal muscles) and in the muscles that maintain upper airway patency (larynx and pharynx) can lead to impaired ventilation and oxygenation, resulting in apneic episodes. Because the respiratory system is immature, suck and swallow activity during feeding may also cause apnea and bradycardia. This is primarily because of inhibitory

reflexes triggered by laryngeal receptors (Reference 19). Furthermore, premature neonates have a reduced lung volume, triggering periods of hypoventilation or oxygen desaturation and apnea (Reference 6).

Prolonged apnea will cause a significant decrease in ventilation and subsequent decrease in heart rate. In very premature infants, apnea and bradycardia episodes may precede hypoventilation and oxygen desaturation (Reference 19). Ventilation-perfusion (V/Q) match is optimum when the ratio of volume of gas to volume of blood in the lungs is equal. Periods of hypoventilation could lead to V/Q mismatching, also resulting in oxygen desaturation. The relationship between apnea, oxygen desaturation, and bradycardia is schematically shown in Figure 1.

Classifications

The three classifications for apneic episodes are (1) central, (2) obstructive, and (3) mixed. The absence of airflow movement is observed with central apneas, whereas reduced or no airflow caused by upper airway obstruction is observed with obstructive apneas. Mixed apnea is a combination of these effects in which apnea follows airway obstruction with persistent inspiratory efforts (Reference 20). Apnea lasting longer than 20 seconds is very often accompanied by airway obstruction (Reference 21).

One study reviewed 2082 apneic episodes lasting more than 15 seconds in 47 infants younger than 34 weeks' gestational age with idiopathic AOP (Reference 22). The investigators identified that 40% of these episodes were central, 50% were mixed, and 10% were obstructive. A correlation existed with decreased oxygen saturation and increased duration of apnea regardless of the type of apnea or treatment. Infants with central apneas had a higher incidence of bradycardia than infants having mixed or obstructive apneas.

Clinical Presentation

Apnea of prematurity presents as a transient cessation in respiratory airflow. These short breathing pauses can persist for 5–20 seconds or more. After about 20 seconds of hypoventilation or apnea, the infant progresses to hypoxemia and ultimately bradycardia and cyanosis. Pallor and hypotonia may occur after 30–45 seconds of no airflow (Reference 23). All premature infants younger than 35 weeks' gestational age should be monitored for AOP within the first week of life.

Premature infants who are spontaneously breathing without mechanical respiratory support typically present with apnea on the first or second day of life. Infants who require mechanical ventilation at birth may not show symptoms of AOP until ventilator support is discontinued (Reference 24). Apnea presenting after the first week of life in infants who are spontaneously breathing or apnea recurring after 1–2 weeks of an apnea-free period is often associated with a serious underlying condition (such as sepsis or necrotizing enterocolitis), warranting a thorough evaluation for precipitating causes (Reference 10).

Diagnosis

No objective threshold criteria or diagnostic tests currently exist for the diagnosis of AOP. Consequently, the diagnosis is one of exclusion in which causes of secondary apnea should be excluded before initiating treatment

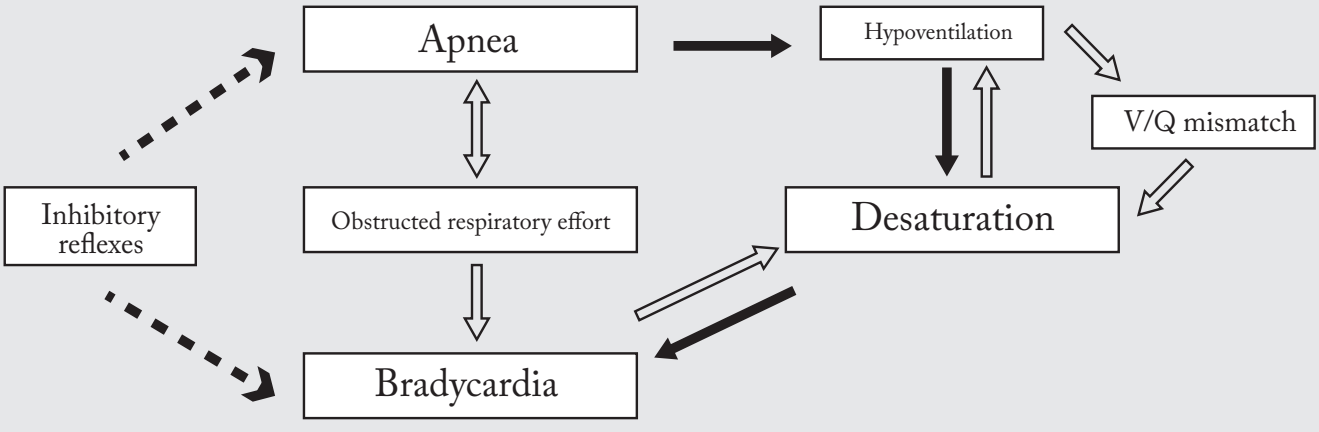


Figure 1. Pathogenesis of apnea of prematurity. Filled arrows represent the most common sequence.

Reprinted by permission from Macmillan Publishers Ltd: Mathew OP. Apnea of prematurity: pathogenesis and management strategies. J Perinatol 2001;31:302–10 (Reference 15).

for AOP (Reference 9). An extensive evaluation of apneic episodes is required to rule out other conditions (refer to Box 1) to accurately diagnose AOP (Reference 25). Pertinent patient history should include a review of maternal risk factors, medications, and birth history. Findings of lethargy, temperature instability, cyanosis, and respiratory distress are observed through a physical examination. Laboratory studies should include serum electrolytes to rule out metabolic disturbances, a complete blood cell count with differential and platelet count to rule out sepsis and anemia, and an arterial blood gas for evidence of hypoxia. A thorough workup is necessary to identify the precipitating cause of apnea, if present.

If apneic events are persistent and a specific cause has not been identified, electronic cardiorespiratory monitoring may be necessary (Reference 3). Individual apneic episodes are often detected by the presence of three primary symptoms: (1) apnea lasting greater than 20 seconds, (2) bradycardia based on cardiorespiratory monitoring, and (3) oxygen desaturation based on pulse oximetry (References 19, 20). Evaluation should also include an assessment of breathing regulation while the neonate is sleeping, feeding, and awake. The severity of AOP and the threshold for initiating or adjusting treatment depend on the frequency and severity of clinically observed apneic episodes (Reference 9).

Monitoring and Evaluations

It is recommended that all premature neonates younger than 35 weeks' gestational age be monitored for at least 1 week after birth because of the higher risk of apneic episodes in this population (Reference 26). Cardiorespiratory monitoring should be performed while the neonate is in the hospital, with assessment during different phases of sleeping, feeding, and alertness. Tactile stimulation usually resolves most apneic episodes in premature neonates. However, some neonates may require assistance with ventilation using a bag and mask when they do not respond to stimulation (Reference 26).

Box 1. Risk factors for apnea in a neonate (Reference 6).

Common Causes of Neonatal Apnea

Prematurity
Airway abnormalities
Gastroesophageal reflux
Hypoglycemia
Impaired oxygenation
Infection (sepsis, meningitis)
Intracranial pathology (hemorrhage)
Medications (opiates, general anesthesia)
Metabolic disorders (acidosis, electrolyte disturbances)
Maternal drugs (antepartum magnesium sulfate, opiates)
Perinatal asphyxia
Seizures
Temperature instability

Therapy Goals

The primary goal of therapy is to decrease or eliminate the frequency of prolonged apnea lasting greater than 20 seconds or apnea associated with cyanosis and bradycardia. Other causes of apnea must be excluded, and the diagnosis of AOP should be made before initiating an individualized treatment. Treatment is warranted in premature neonates if apneic episodes are frequent and prolonged or if they are associated with hypoxemia and bradycardia (Reference 25). The premature neonate will usually require several weeks of therapy until lung function matures and apnea resolves (References 8, 10). Because apnea is multifactorial in pathophysiology and presentation, a single intervention may not be entirely efficacious, and both nonpharmacologic and pharmacologic therapies may be required for the treatment of AOP.

Nonpharmacologic Therapy

Because a potential cause of apneas is hypoxemia, it would be reasonable to initiate therapies to improve oxygenation. Supplemental oxygen works to decrease the frequency of hypoxic episodes (Reference 27). Although few approaches have been studied in clinical trials, oxygen saturations generally should be maintained between 85% and 95% to minimize the complications of oxygen toxicity such as retinopathy of prematurity (Reference 28). In addition, transfusion of red blood cells can increase the blood-carrying oxygen capacity, but this treatment approach remains controversial. Cohort studies reporting variable differences in the frequency, severity, or duration of apnea after a blood transfusion are conflicting (References 29, 30). However, blood transfusions may be considered if the infant also has other comorbidities such as anemia of prematurity, which is common among premature neonates. Therefore, the potential benefits gained from a transfusion should be outweighed against the complications and hazards of this therapy.

If the cause of apnea is airway obstruction and hypoventilation, strategies to maintain airway patency may be beneficial. For example, positions of extreme flexion or extension of the neck can contribute to upper airway obstruction; thus, they should be avoided (Reference 26). Nasal patency can be preserved by avoiding unnecessary nasal suctioning or nasogastric tubes. Other general measures include preventing reflexes that could trigger apnea and maintaining a stable environmental temperature using a radiant warmer or incubator (Reference 26).

Continuous positive airway pressure (CPAP), a method of assisted respiratory ventilation often administered with nasal prongs, is effective in decreasing the incidence of mixed and obstructive apnea by opening the upper airways (Reference 27). This method is most useful in neonates younger than 32–34 weeks' postmenstrual age and those with residual lung disease because these groups are most susceptible to pharyngeal collapse (References 27, 31, 32).

If clinically significant apneic episodes accompanied by bradycardia and cyanosis still occur despite optimal drug therapy and CPAP, endotracheal intubation and assisted ventilation may be required as a last-line therapy. This method is not often necessary for the treatment of AOP unless other illnesses such as sepsis or meningitis are present (Reference 26). If significant obstructive or mixed apneic episodes are unresolved, pharmacologic therapy aimed at treating central apneas is essential and should be used in conjunction with nonpharmacologic interventions.

Pharmacologic Therapy

Methylxanthines

Methylxanthines, a group of purine alkaloids, have been the mainstay of therapy for AOP since the early 1970s (Reference 33). They stimulate the central respiratory drive to reduce the incidence of apneas and need for mechanical ventilation (References 9, 34). The most common agents include caffeine citrate, theophylline, and aminophylline (a theophylline salt). Controlled studies comparing aminophylline, theophylline, and caffeine have found them to be comparable in efficacy for the control of AOP (References 35, 36). However, caffeine remains the standard therapy because of its wide therapeutic index, ease of administration, tolerability, and limited adverse effects. Theophylline and aminophylline are rarely used in clinical practice but are potential alternatives if infants are refractory to caffeine therapy.

Mechanism of Action

Although methylxanthines are frequently used and have been shown to be effective, their exact mechanism of action in the treatment of AOP is unclear. It is proposed that methylxanthines stimulate the central nervous system, increase carbon dioxide sensitivity, and enhance the force of diaphragmatic contraction (Reference 9). There is also some action on the cardiovascular system to increase cardiac output and heart rate while decreasing peripheral vascular resistance (Reference 37).

Methylxanthines are nonspecific inhibitors of adenosine and phosphodiesterase. Adenosine acts to depress the central respiratory drive. Because methylxanthine blocks the action of adenosine, the respiratory drive is enhanced to reduce apneic episodes in neonates (Reference 38). Meanwhile, phosphodiesterase inhibition results in increased levels of cyclic adenosine monophosphate and cyclic guanine monophosphate to relax the airway (References 39, 40). The combined effects of adenosine and phosphodiesterase inhibition stimulates the central respiratory center to enhance ventilation and blood gas exchange, increase diaphragmatic contractility, and improve upper airway muscle tone (Reference 9).

Pharmacokinetics and Dosing

Pharmacokinetic parameters vary widely in premature and term infants and exhibit high inter-individual variability due to developmental changes in metabolism and excretion (Reference 41). Caffeine and theophylline are extensively metabolized in the liver by cytochrome P450 (CYP) monooxygenases (CYP1A2) and xanthine oxidase (Reference 37). Metabolism is limited in premature infants because of an immature hepatic enzyme system, but it increases significantly with postnatal age. Metabolic interconversion of active metabolites has been observed in infants. An estimated 3% to 8% of administered caffeine is converted to theophylline, and 25% of administered theophylline is converted to caffeine (Reference 42).

Renal excretion is the primary mechanism of elimination for methylxanthines. In infants, around 80% of caffeine and its metabolite, theophylline, is excreted unchanged in the urine (References 43, 44). The half-life of each drug is highly variable and generally decreases in term infants and with postnatal age. Caffeine has an elimination half-life of 52–96 hours compared with theophylline, with a half-life of 17–43 hours in premature infants (References 42, 44, 45). The longer half-life of caffeine allows for once-daily dosing, which offers an advantage over the multiple-daily dosing required with theophylline and aminophylline. Most studies also recommend a loading dose followed by a maintenance dose. Table 1 lists additional dosing and pharmacokinetic differences between caffeine citrate, theophylline, and aminophylline in neonatal apnea.

Therapeutic Drug Monitoring

Theophylline at the desired plasma concentrations of 6–12 mg/L provides an adequate clinical response in most infants, although lower concentrations of 3–4 mg/L have also been reported to be effective (Reference 46). The unbound fraction of theophylline is the pharmacologically active compound. Although a neonate and an adult may have the same total theophylline plasma concentration, the unbound concentration is generally higher in the neonate because of reduced protein binding. Therefore, measuring unbound serum

theophylline levels is recommended in neonates (Reference 47). The narrow therapeutic index requires frequent therapeutic drug monitoring of theophylline to prevent adverse effects or suboptimal therapy.

Theophylline plasma concentrations are recommended before and after a dosage adjustment, after treatment failure such as an increased frequency of apneas, or with evidence of toxicity (References 44, 45). Doses should be individualized on the basis of peak levels measured 30 minutes after the end of the bolus infusion and at steady-state concentration, usually after 3 days of therapy. Repeat levels are indicated around 3 days after each dosage titration or weekly if the infant is on a stable maintenance dose (Reference 45). Of importance, patient factors that could potentially affect the clearance and metabolism of theophylline should be carefully observed (Reference 48). For example, anticonvulsants such as phenytoin and phenobarbital are CYP-inducing agents that can decrease the plasma concentration of theophylline (Reference 49). Because of the substantial individual variability in pharmacokinetics, narrow therapeutic index, and severe toxicity profile with theophylline, therapeutic drug monitoring should be closely followed.

Caffeine, by contrast, exhibits a wide therapeutic index, with plasma concentrations ranging from 8 mg/L to 20 mg/L. Serious toxicities are rare but have been reported with concentrations greater than 40 mg/L to 50 mg/L (References 34, 50). Most infants are predicted to reach a therapeutic plasma concentration using the standard recommended caffeine citrate dosing (Table 1). After an oral loading dose of caffeine citrate of 20 mg/kg in preterm neonates, the measured peak plasma concentration for caffeine ranged from 6 mg/L to 10 mg/L (Reference 42). In an observational study of 101 infants, a median caffeine maintenance dose of 5 mg/kg resulted in caffeine levels from 3 mg/L to 23.8 mg/L. About 95% of samples resulted in levels between 5 mg/L and 20 mg/L, and similar results were observed in patients with renal and liver dysfunction (Reference 51). If clinical response is lacking at high doses or toxicity is suggested, a therapeutic plasma concentration may be considered, but routine monitoring of concentrations is not typically necessary. The wide therapeutic index without the need to closely follow serum drug levels makes caffeine the therapy of choice for AOP.

Duration of Therapy

The necessary duration of therapy is highly variable in neonates with AOP and is dependent on the maturity of the brainstem and respiratory control system. Caffeine therapy should be continued until there are no clinically observed apneic episodes for several consecutive days, which is generally observed before 37 weeks' postmenstrual age (References 9, 26). Because of the long elimination half-life, cardiorespiratory monitoring should continue for about 1 week after discontinuing therapy until the drug is completely eliminated from the body (Reference 26). Consider reinitiating therapy if apnea recurs soon after therapy discontinuation.

Table 1. Dosing and Pharmacokinetics of Caffeine, Theophylline, Aminophylline, and Doxapram in AOP (References 42, 44, 45)

	Caffeine Citrate	Theophylline, Aminophylline	Doxapram
Route of administration	Oral, intravenous	Oral, intravenous	Intravenous
Loading dose	20–25 (10–12.5 active base) mg/kg/dose	5–6 mg/kg/dose	2.5–3 mg/kg/dose
Maintenance dose	5–10 (2.5–5 active base) mg/kg/day	2–6 mg/kg/day	1 mg/kg/hour
Dosing interval	Every 24 hours	Every 8–12 hours	Continuous infusion
Therapeutic plasma concentration (mg/L)	8–20	6–12	Unknown
Toxic plasma concentration (mg/L)	> 50	> 15	Unknown
Elimination half-life (hours)	52–96	17–43	6–12
Signs of toxicity	Failure to gain weight Jitteriness Hyperreflexia Seizures	Restlessness Vomiting Arrhythmias	Hypertension Skeletal muscle hyperactivity

AOP = apnea of prematurity.
Note: When converting from intravenous to oral aminophylline, increase the dose by 20%. No dose change is required when converting from intravenous aminophylline to oral theophylline.

Clinicians will usually assess postmenstrual age, length of time since the last documented apneic episode, and general clinical status to determine when to discontinue therapy (Reference 9).

Adverse Effects

Methylxanthines are generally a safe therapy if caffeine is prescribed within the usual recommended dosing range and theophylline plasma concentrations are carefully monitored. Adverse effects of methylxanthine treatment may include feeding intolerance, sinus tachycardia, diuresis, diaphoresis, and urinary calcium excretion. Severe toxicity can be manifested as hypertonia, cardiac failure, pulmonary edema, metabolic acidosis, and hyperglycemia (References 42, 44, 45). These adverse effects are more commonly observed with theophylline than with caffeine. In addition, dosing changes because of an adverse effect are less likely with caffeine therapy (Reference 52).

Caffeine for AOP Trials

A landmark randomized controlled trial of caffeine citrate in 2006 infants with birth weights of 500–1250 g evaluated the short- and long-term safety and efficacy of methylxanthine therapy (Reference 53). Caffeine citrate was indicated for the prevention or treatment of AOP and the facilitation of endotracheal tube removal. Eligible patients received an intravenous loading dose of caffeine citrate of 20 mg/kg, followed by a maintenance dose of 5 mg/kg or normal saline. The daily maintenance dose was increased to a maximum of 10 mg/kg if apneas persisted. Caffeine was initiated at a median postmenstrual age of 28 weeks and discontinued before 35 weeks of age. The caffeine group discontinued adjunct nonpharmacologic treatments, such as mechanical ventilation and oxygen therapy, 1 week earlier than the placebo group. In addition, the frequency of bronchopulmonary dysplasia, a chronic lung disease of prematurity, was significantly reduced in the caffeine group, 36.3% compared with 46.9%.

The long-term follow-up study at 18–21 months included 937 infants in the caffeine group and 932 infants in the placebo group (Reference 54). Among the primary outcomes assessed were a composite of death, cerebral palsy, cognitive delay, deafness, or blindness at a corrected age of 18–21 months. Significantly fewer infants in the caffeine group died or survived with a neurodevelopmental disability compared with the placebo group (40.2% vs. 46.2%). Treatment with caffeine also showed a reduction in the incidence of cerebral palsy (4.4% vs. 7.3%) and cognitive delay (33.8% vs. 38.3%). There were no differences in rates of death, deafness, and blindness or mean percentiles for height, weight, and head circumference at follow-up between the caffeine and placebo groups.

These trials provide strong evidence that caffeine citrate is a beneficial therapy for AOP. A loading dose of caffeine citrate followed by maintenance dosing has shown favorable short- and long-term outcomes with minimal adverse effects. It also improves survival without neurodevelopmental disability. Although aminophylline, theophylline, and caffeine show similar efficacy for the treatment of AOP, caffeine has been the most rigorously studied and is the mainstay treatment for AOP in clinical practice. It is the preferred pharmacologic treatment for its lower toxicity and longer half-life without the need for routine therapeutic drug monitoring.

Doxapram

Doxapram is one of the first drugs investigated for the treatment of AOP. It is a potent respiratory stimulant that acts on peripheral chemoreceptors and the respiratory center in the medulla (Reference 9). Doxapram has been used in infants with AOP refractory to methylxanthine therapy. Early trials have shown doxapram to be effective in treating infants with neonatal apnea who are unresponsive to methylxanthine therapy (References 55, 56). However, these studies were small, and additional information is needed to define the role of doxapram in the treatment of AOP. The usual dosing for doxapram infusions ranges from 0.5 to 2 mg/kg/hour (Table 1). The lowest effective dose of doxapram should be used initially and titrated upward based on clinical response.

The commercially available intravenous formulation of doxapram contains benzyl alcohol, a preservative associated with a potentially fatal toxicity known as "gasping syndrome" in neonates, and should be used with caution (Reference 57). Other important adverse effects include hypertension, seizures, cardiac conduction disorders, hypoglycemia, and gastric irritation (Reference 9). Overall, there is a paucity of data on the tolerability, efficacy, and pharmacokinetics of doxapram. Until larger, controlled trials are available, doxapram should not be used for the treatment of AOP (Reference 58).

Discharge Planning

Most premature neonates will have resolution of AOP symptoms at 34–36 weeks' postmenstrual age (Reference 9). However, some infants, especially those at gestational ages younger than 28 weeks, may continue to have persistent apneic episodes beyond 38 weeks' postmenstrual age when they may be otherwise ready for discharge (Reference 8). There are no defined treatment guidelines for these infants, but the goal is aimed at reducing the risk and incidence of the apneic episodes so that the infant may be cared for at home. A major dilemma in the

management of AOP is deciding whether to continue methylxanthine therapy after discharge or to delay discharge until apnea completely resolves. The decision to provide a home apnea monitor or to continue methylxanthine after discharge should be individualized for each patient. It is difficult to establish the minimum number of symptom- and treatment-free hospital days to ensure an absence of apneic episodes after discharge.

In a retrospective study of premature infants younger than 32 weeks' gestational age and weighing less than 1500 g at birth, the investigators observed that an 8-day absence of symptoms of apnea, bradycardia, and/or color change was a good predictor of AOP resolution (Reference 59). However, published literature does not clearly indicate whether hospital discharge should be delayed or whether AOP treatment and monitoring should be continued at home. The clinician should exert judgment when making this decision on the basis of the infant's history and presentation.

Conclusions

Apnea is a significant problem for premature infants. Unfortunately, a standard treatment guideline for AOP is currently unavailable. A careful assessment of the infant is necessary to identify the etiology and an individualized treatment plan. Although several nonpharmacologic and pharmacologic treatment strategies exist, the clinician must carefully weigh the risks and benefits associated with each treatment modality. Caffeine is the optimal pharmacologic treatment strategy for AOP for its favorable pharmacokinetic safety profile and long-term outcomes. Infants treated with caffeine have fewer incidences of bronchopulmonary dysplasia and better neurodevelopmental outcomes. Apnea of prematurity can have an excellent prognosis with appropriate management and recognition of symptoms.

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CHAPTER 14

Pediatric Asthma

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Learning Objectives

1. Define asthma and describe its epidemiologic prevalence on the basis of risk factors, genetics, and population characteristics.
2. Explain the underlying pathology that results in disordered lung function and recognize the associated symptoms and diagnostic criteria of asthma.
3. Classify asthma on the basis of severity and control to develop an approach to effective management.
4. Evaluate nonpharmacologic and pharmacologic therapies for their effect and mechanism in reducing impairment and risk of asthma.
5. Develop an understanding of available therapy and appropriate use of delivery devices to maximize therapeutic outcomes and medication safety and to reduce risk of asthma.

Abbreviations in This Chapter

FEV_1	Forced expiratory volume in 1 second
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
LABA	Long-acting β-agonist
NAEPP	National Asthma Education and Prevention Program
SABA	Short-acting β-agonist

Introduction

Asthma, the most common chronic disease in childhood, is an inflammatory disease of the airways caused by a complex interaction of factors. Asthma is characterized by symptoms occurring in paroxysms that are usually related to specific triggering events, airway narrowing that is partly or completely reversible, and increased airway responsiveness to a variety of stimuli (Reference 1). Inflammation and airflow obstruction, which are often reversible, cause episodes of cough, wheezing, dyspnea, and chest tightness. Despite the long history since the disease was first recognized, the development of a greater understanding of asthma etiology and treatment has recently occurred.

In 1991, the National Heart, Lung, and Blood Institute of the National Institutes of Health published the first Expert Panel Report on asthma, which established guidelines for asthma diagnosis and management. Significant advances have been made since the release of the first clinical practice guidelines, with a decline in the number of deaths caused by asthma despite increasing prevalence, decrease in reports of activity limitation by patients with asthma, and increased proportion of people with asthma who receive formal patient education (Reference 2). Despite advances in and availability of medical interventions that help prevent morbidity and improve quality of life, the unknown cause, complex disease development, and the burden of prevalence, resource use, and mortality continue to pose a significant problem in public health.

Epidemiology

The epidemiology of asthma is difficult to define given the lack of a standard definition and methods used to identify affected individuals in epidemiologic studies (Reference 3). Despite these epidemiologic challenges and the wide global variation in the prevalence of asthma, it is one of the leading chronic childhood diseases in the United States (Reference 4).

Asthma Prevalence and Mortality

The recent estimated worldwide asthma prevalence is 7% to 10%, with more than 300 million people affected. Prevalence has more than doubled from 1980 to the mid-1990s in the United States alone according to available and published data, with the number of children who currently have asthma in the United States estimated to be 7.1 million (Reference 5).

Asthma prevalence across the world is disparate, with a trend toward higher prevalence in developed countries. Although westernization may account for some of the differences in prevalence by country, these differences may be explained by variability in genetic, social, and environmental risk factors (Reference 6).

Asthma leads to about 250,000 deaths worldwide each year. Annual death rate from asthma in the United States increased from 1982 to 1995, but it has declined each year since, according to surveillance and epidemiologic data (Reference 7).

Demographic Characteristics

Among children aged 0–17, asthma affects more males than females (11.3% vs. 7.9%, respectively). Asthma prevalence increases with age, though health care use is highest among the youngest children (Reference 7). The racial disparity in asthma prevalence and health care resource use is extensive. Black and Puerto Rican children have the highest prevalence rates compared with children of other races, whereas Asian children have the lowest prevalence rates. The higher rates of emergency department visits, hospitalizations, and deaths among minority children have been well documented. The disparity in asthma mortality between black and white children has increased in recent years, with black children having higher mortality rates (Table 1).

Etiology

Pathophysiology

Asthma is a complex, inflammatory disease process with physiologic reduction in airway luminal diameter, which is critical to the flow of air in the lungs. The relationship between luminal diameter and resistance can be explained with Poiseuille's law, which is based on the physical principle that resistance is inversely proportional to flow; therefore, the greater the resistance, the less the flow.

Poiseuille's law

$$R = \frac{8nl}{\pi r^4}$$

R = resistance
n = viscosity of air
l = length of tube
r = radius of tube

Given that the viscosity of air (n) and the length of the tube (l) remain relatively constant in the lung, the radius (r) has a dramatic effect on resistance to airflow. For example, if there is a 50% decrease in the radius of an airway, the resistance to airflow increases by a factor of 16. Therefore, Poiseuille's law is paramount to understanding the impact of the inflammatory processes and airway narrowing in asthma on airflow.

The pathophysiology of asthma is characterized by airway and bronchial hyperresponsiveness, bronchoconstriction, and airway inflammation involving inflammatory cells and mediators (Reference 1). Airway and bronchial hyperresponsiveness, defined as the degree to which airways narrow in response to a nonspecific stimulus or an environmental trigger, correlates with asthma severity in children (References 7–9). Reversible bronchoconstriction and bronchospasm result from bronchial smooth muscle contraction in response to a variety of stimuli. The episodic and sudden onset of bronchoconstriction is commonly referred to as an "asthma attack," the dominant physiologic event leading to clinical symptoms. The continuous underlying airway inflammation has a central role in the disease pathophysiology, causing epithelial cell damage and increased mucosal permeability (References 10–12). Airway inflammation is evidenced by the presence of inflammatory cells (neutrophils, eosinophils, T lymphocytes, alveolar macrophages, and mast cells); mediators (leukotrienes, histamine, prostaglandins, thromboxanes, platelet-activating factor, and adhesion molecules found in bronchoalveolar lavage fluid); immunoglobulin E (IgE) antibodies, which are linked to the progression of lung disease; and exaggerated inflammatory response, which is associated with impaired glutathione homeostasis, a biomarker of oxidant stress (References 13–15).

In addition, many pathologic changes are reflected in the sputum, including Charcot-Leyden crystals (eosinophil remnants), Curschmann spirals (airway lumen casts of exudate), and Creola bodies (clumps of sloughed epithelial cells) (Reference 16). A histologic examination of asthmatic lungs shows hyperplasia and hypertrophy of airway smooth muscle, increased airway wall thickness, and mucous gland hypertrophy and mucus hypersecretion.

Genetic Basis

Complex interactions between genetics and environmental influences contribute to asthma as an inflammatory disease. Epidemiologic studies suggest a genetic predisposition to asthma development because twins and families show patterns of disease consistent with heritable factors (References 17–19). In fact, studies of twins suggest that genetic factors account for 50% of susceptibility (Reference 20). Some components of the asthma phenotype appear strongly heritable, although the genes responsible for these components remain to be identified, and inheritance does not follow the mendelian pattern of genetics. The genetic predisposition for developing an IgE-mediated response to common aeroallergens, known as atopy, remains the strongest identifiable predisposing factor for developing asthma (Reference 1). The hygiene hypothesis states that lack of exposure to infectious agents and microorganisms in early childhood increases the susceptibility to allergic diseases, including asthma, by suppressing appropriate immune system development and response.

Risk Factors for Disease

The host and environment play a significant role in the risk of developing asthma. Table 2 lists the host factors and environmental factors that have been associated with asthma development (References 1, 5, 21–25).

Table 1. Asthma Prevalence and Mortality Among Children 0–17 Years of Age by Race and Ethnicity, United States, 2003–2005

Race and Ethnicity	Current Prevalence, % (2004–2005)	Deaths per 1,000,000 (2003–2004)
Race only		
White	7.9	1.5
Black	12.8	9.0
American Indian or Alaska Native	9.9	–
Asian	4.9	–
Race/ethnicity		
Hispanic	7.8	1.8
Puerto Rican	19.2	–
Mexican	6.4	1.7
Non-Hispanic white	8.0	1.3
Non-Hispanic black	12.7	9.2
Total	8.7	2.6

– = no data.
Adapted from Akinbami LJ. The State of Childhood Asthma, United States, 1980-2005. Advance Data from Vital and Health Statistics, No. 381. Hyattsville, MD: National Center for Health Statistics, 2006.

Table 2. Factors Associated with Asthma

Host Factors	Environmental Factors
▪ Genetics ▪ Innate immunity o Atopy – rhinitis and dermatitis o Hygiene hypothesis – lack of early childhood infection modifies immune response and reduces tendency to produce IgE antibodies to environmental allergens ▪ Race/ethnicity ▪ Sex	▪ Urbanization and socioeconomic status ▪ Allergens: house dust mites, animal proteins (cat and dog allergens), cockroaches, fungi ▪ Endotoxin exposure – inflammatory lipopolysaccharide molecules from gram-negative bacteria ▪ Respiratory infections – particularly viral infections (RSV and rhinovirus) ▪ Others: tobacco smoke, pollutants (may be caused by specific pollutants [CO, NO_2, SO_2])

IgE = immunoglobulin E; RSV = respiratory syncytial virus.

In addition to the risk factors for disease, predictors of asthma include family history of asthma, eczema, and/or smoking; history of allergic rhinitis, sinusitis, nasal polyps, eczema, or bronchopulmonary dysplasia; and recurrent cough, bronchitis, and bronchiolitis (References 1, 26–28).

Clinical Presentation and Diagnosis

Signs and Symptoms

The symptoms of asthma result from airflow obstruction and the cumulative effects of smooth muscle constriction around airways, airway wall edema, intraluminal mucus accumulation, inflammatory cell infiltration of the submucosa, and basement membrane thickening (References 10–12). Inflammation causes recurrent episodes of dyspnea, cough, and wheezing that can be nonspecific, making asthma difficult to distinguish from other respiratory diseases in the pediatric patient. Older children may experience shortness of breath and chest tightness, whereas younger children may have nonfocal chest pain. In addition, younger children may have more subtle symptoms such as decreased physical activity, general fatigue, and difficultly keeping up with peers.

Asthma exacerbations are associated with widespread but variable airflow obstruction and are often reversible with or without treatment. Life-threatening asthma is a constellation of symptoms that can occur in any patient with asthma; these symptoms include the following (Reference 1):

- Marked chest tightness
- Wheezing, severe shortness of breath

- Retractions
- Cyanosis
- Inability to speak or speak in sentences because of dyspnea
- Hunched posture
- Altered mental status (agitation, anxiety, lethargy)

Diagnostic Criteria

The initial diagnosis of asthma in children is often difficult and requires the exclusion of other diagnoses. Clinical history or presence of respiratory symptoms consistent with asthma, combined with the demonstration of variable expiratory airflow obstruction is required for the diagnosis of asthma. Asthma diagnostic criteria include history, physical examination, pulmonary function testing, and laboratory evaluations (Reference 1). Comorbid conditions associated with asthma include gastroesophageal reflux disease, obstructive sleep apnea, obesity, rhinitis, and sinusitis (References 1, 29, 30).

A detailed clinical history involves assessing the patient for cough, wheeze, shortness of breath, and/or chest tightening that occurs in an "episodic" fashion. These symptoms may occur or worsen with exercise, weather changes, night hours, viral infection, inhalant trigger exposure (smoke, fur, dust mites, mold, pollen), irritant trigger exposure (e.g., airborne chemicals [aerosols], smoke), strong emotional expressions (laughing, crying), and menstrual cycles (References 1, 31–34).

The physical examination should assess for severity of respiratory symptoms; rhinitis, increased nasal secretions, mucosal swelling, or nasal polyps; and presence of airflow obstruction or airway hyperresponsiveness that is partly reversible (e.g., spirometry shows a percent change in forced expiratory volume in 1 second [FEV_1] of 12% or more from baseline or 10% or more of predicted after the patient inhales a short-acting bronchodilator) (References 1, 35). To establish the diagnosis and facilitate severity assessment, the National Asthma Education and Prevention Program (NAEPP) recommends spirometry in children older than 5 years. In infants and children younger than 5 years, the diagnosis centers on the same evaluation as discussed, although spirometry often cannot be performed in this age group because of developmental ability (e.g., ability to breathe in and exhale fully). Debate is ongoing about how best to diagnose and classify infants and young children with recurrent wheezing.

Tests to exclude other diagnoses when the history and physical examination are equivocal include a chest radiograph, bronchoprovocation test, and allergen testing (eosinophilia, total IgE, rarely aspergillosis) (Reference 1).

Disease Course and Prognosis

The progression of asthma is marked and measured by decline in lung function (Reference 1). Reduction in the FEV_1/forced vital capacity ratio is evidenced in children who have mild or moderate asthma compared with children who do not have asthma. According to longitudinal epidemiologic studies and clinical trials, the characteristic decline in lung function varies by age group. Children with symptoms before 3 years of age show a decline in lung function growth by 6 years of age, but children 5–12 years of age who have mild or moderate persistent asthma usually have no decline in lung function through 17 years of age, although a subset of children experience progressive reductions in lung growth.

In addition to the natural progression of asthma, other factors place patients at risk of asthma-related death. These include comorbid conditions such as heart or lung disease; previous severe exacerbation (e.g., intubation or intensive care unit admission); two or more hospitalizations or more than three emergency department visits in the past year; use of more than one canister of short-acting β-agonist (SABA) per month; difficulty perceiving airway obstruction or the severity of worsening asthma (parent and/or child); low socioeconomic status or inner-city residence; illicit drug use; and major psychosocial problems or psychiatric disease (References 1, 36).

Asthma Severity and Control

Asthma severity is determined by a constellation of impairment and risk and is defined along a continuum from intermittent, mild persistent, moderate persistent, and severe persistent asthma. In addition to patient history, the tools used to assess severity through measures of lung function are performed by spirometry for children 5 years and older (FEV_1), pulmonary function testing, and airway hyperresponsiveness testing using methacholine (References 1, 35). A patient's level of control is determined at follow-up visits on a scale of well, poorly, and very poorly controlled as well as on the basis of the domains of impairment and risk. Asthma severity and control are used to determine the recommended step for initial and stepwise therapy, which are discussed in the subsequent "Treatment" section of this chapter.

Treatment

Therapy Goals

The NAEPP has defined the primary goal of asthma management as "asthma control," which involves a reduction in both impairment and risk (Reference 1).

The reduction in frequency and severity of asthma exacerbations and long-term sequelae should be achieved by maintaining asthma control with the fewest therapeutic interventions possible. Intensive education and monitoring are required in caring for all children with asthma and are discussed further in sections below (References 1, 22, 23, 37).

Nonpharmacologic Therapy

The primary principles of nonpharmacologic therapy and cornerstone to asthma management are patient/caregiver education and self-management. Nonpharmacologic therapy seeks to control exposure to environmental factors, reduce risk from comorbid conditions, and allow appropriate use of therapy and health care resources. Evidence suggests that educational interventions improve asthma outcomes. Table 3 lists the key components to asthma education (References 1, 37–39).

Other suggested nonpharmacologic therapies include breathing techniques (Buteyko breathing technique, Papworth method, and yoga breathing [pranayama]), acupuncture, relaxation techniques (meditation, biofeedback, hypnosis, and progressive muscle relaxation), herbal remedies (butterbur, dried ivy, and ginkgo extract), omega-3 fatty acids, and homeopathy, though not well established (Reference 1).

Pharmacologic Therapy

Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations, and reverse airflow obstruction. Tables 4–6, adapted from the NAEPP Guidelines for the Diagnosis and Management of Asthma, show the classification of asthma severity and assessment of asthma control, each of which guide therapy initiation and subsequent stepwise adjustment of medications for asthma management (Reference 1). To initiate pharmacologic therapy, asthma severity is first classified into intermittent or persistent asthma (Table 4) on the basis of symptoms during the specified time. On the basis of the severity classification, the appropriate step for therapy initiation is determined. Then, on the basis of an assessment of asthma control (Table 5), an action for treatment is recommended within the stepwise management approach. The specific

Table 3. Key Components of Patient and Family Asthma Education

Basic Facts	Role of Medications	Patient Skill Set
▪ The contrast between the airways of a person who has and a person who does not have asthma ▪ The role of inflammation ▪ What happens to the airways during an asthma attack?	▪ Long-term control medications: Prevent symptoms, often by reducing inflammation. Must be taken daily ▪ Quick-relief medications: SABAs relax airway muscles to provide prompt relief of symptoms. *Note: Use of SABAs > 2 days/week to relieve asthma symptoms suggests the need to reassess asthma control and consider escalation of therapy.*	▪ Self-monitoring o Self-assessment of level of asthma control o Monitoring symptoms and, if prescribed, peak expiratory flow measures o Recognizing symptom patterns and early signs and symptoms of worsening asthma o Use of a written asthma action plan to know when and how to - Take daily actions to control asthma - Adjust medication(s) early in response to signs of worsening asthma - Seek medical care as directed - Value of adherence and periodic monitoring to adjust therapy ▪ Taking medications correctly ▪ Inhaler technique (demonstration/return demonstration) ▪ Use of devices as prescribed (valved holding chamber or spacer, nebulizer) ▪ Identifying and avoiding triggers that worsen the patient's asthma (allergens, irritants, tobacco smoke)

SABA = short-acting β-agonist.
Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

Table 4. Classifying Asthma Severity and Initiating Therapy

Components of Severity		Intermittent	Persistent		
			Mild	Moderate	Severe
Impairment	Symptoms	≤ 2 days/week	> 2 days/week	Daily	Throughout the day
	Nighttime awakenings	*< 5 years*: 0	*< 5 years*: 1 or 2×/month	*<5 years*: 3 or 4×/month	*<5 years*: > 1×/week
		≥ 5 years: ≤ 2×/month	*≥ 5 years*: 3 or 4×/month	*≥5 years*: > 1×/week	*≥ 5 years*: Often 7×/week
	SABA use for symptoms	≤ 2 days/week	> 2 days/week	Daily	Several times per day
	Limitation of normal activity	None	Minor	Some	E×treme
	Lung function[a]	*5–11 years*: FEV_1 > 80% FEV_1/FVC > 85%	*5–11 years*: FEV_1 ≥ 80% FEV_1/FVC > 80%	*5–11 years*: FEV_1 60% to 80% FEV_1/FVC 75% to 80%	*5–11 years*: FEV_1 < 60% FEV_1/FVC < 75%
		≥ 12 years: FEV_1 > 80% FEV_1/FVC normal	*≥ 12 years*: FEV_1 ≥ 80% FEV_1/FVC normal	*≥ 12 years*: FEV_1 60% to 80% FEV_1/FVC reduced by 5%	*≥ 12 years*: FEV_1 < 60% FEV_1/FVC reduced > 5%
Risk	Exacerbations requiring oral corticosteroids[b]	0–1×/year	*< 5 years*: ≥ 2× in 6 months requiring steroids *or* ≥ four wheezing episodes a year and lasting > 1 day AND risk factors for persistent asthma		
			≥ 5 years: ≥ 2×/year		
Recommended Step for Initiating Therapy (see Table 6)		Step 1	Step 2	Step 3	*< 5 years*: Step 3 *5–11 years*: Step 3 or 4 *≥ 12 years*: Step 4 or 5

[a]Note that some individuals with smaller lungs in relation to their height may NORMALLY have FEV_1 < 80% and/or FEV_1/FVC < 85%. Lung function measures should be correlated with clinical assessment of asthma severity.
[b]For initial therapy of moderate or severe persistent asthma, consider short course of oral corticosteroids.
FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; SABA = short-acting β-agonist.
Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

step of therapy gives a preferred and alternative treatment for various age groups (Table 6). When following the stepwise approach to therapy, monotherapy is typically initiated; however, it would be reasonable to prescribe a combination product to achieve asthma control.

It is also important to assess the severity of exacerbations because this implicates the clinical course as well as the outcomes (Table 7 and Table 8) (Reference 1). The management of exacerbations depends on the severity, identification of triggers and management of control measures, and therapy initiation and adjustment as appropriate (Table 9) (Reference 1). Management of an asthma exacerbation may occur at home, in the physician's office, or in an urgent care or in-hospital setting. Step therapy can be resumed after recovery from an exacerbation.

Several medications are used in the treatment of asthma and exacerbations. Table 10 and Table 11 provide an overview of the classes of medications, including mechanism of action, indication, and adverse effects, as well as medication dosing based on age category (Reference 1).

Table 5. Assessing Control and Adjusting Therapy

Components of Control		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤ 2 days/week	*< 5 years*: > 2 days/week *5–11 years*: >2 days/week or several times on ≤ 2 days/week *≥ 12 years*: > 2 days/week	Throughout the day
	Nighttime awakenings	*< 12 years*: ≤ 1×/month *≥ 12 years*: ≤ 2×/month	*< 5 years*: > 1×/month *5–11 years*: ≥ 2×/month *≥ 12 years*: 1–3×/week	*< 5 years*: > 1×/week *5–11 years*: ≥ 2×/week *≥ 12 years*: ≥ 4×/week
	Interference with normal activity	None	Some limitation	Extremely limited
	SABA use for symptoms	≤ 2 days/week	>2 days/week	Several times per day
	Lung function[a]	*5–11 years* FEV_1 > 80% FEV_1/FVC > 80% *≥ 12 years*: FEV_1 >80%	*5–11 years*: FEV_1 60% to 80% FEV_1/FVC 75% to 80% *≥ 12 years*: FEV_1 60% to 80%	*5–11 years*: FEV_1 < 60% FEV_1/FVC < 75% *≥ 12 years*: FEV_1 < 60%
Risk	Exacerbations requiring OCS[b]	0–1×/year	*< 5 years*: 2–3×/year *≥ 5 years*: ≥ 2×/year	*< 5 years*: > 3×/year *≥ 5 years*: ≥ 2×/year
	Reduction in lung growth	Requires long-term follow-up		
	Treatment-related adverse effects	Medication adverse effects do not correlate with specific levels of control, but they should be considered in overall assessment of risk.		
Recommended Action for Treatment (see Table 6)		Consider step-down if well controlled for ≥ 3 months	Step up 1 step. Reevaluate in 2–6 weeks.	Consider short-course oral corticosteroid. Step up 1 or 2 steps. Reevaluate in 2 weeks.

[a]Note that some individuals with smaller lungs in relation to their height may NORMALLY have FEV_1 < 80% and/or FEV_1/FVC < 85%. Lung function measures should be correlated with clinical assessment of asthma severity.

[b]For initial therapy of moderate or severe persistent asthma, consider short course of oral corticosteroids.

FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; OCS = oral corticosteroids; SABA = short-acting β-agonist.

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

Table 6. Stepwise Approach to Asthma Management

	Preferred treatment(s)	Alternative treatment(s)
Step 1	SABA PRN	
Step 2	Low-dose ICS	*< 5 years*: Cromolyn *or* montelukast *≥ 5 years*: Cromolyn, nedocromil, LRTA, or theophylline
Step 3	*< 5 years*: Medium-dose ICS *5–11 years*: Low-dose ICS + LABA, LTRA, or theophylline *OR* Medium-dose ICS *≥ 12 years*: Low-dose ICS + LABA *OR* Medium-dose ICS	*≥ 12 years*: Low-dose ICS + LRTA, theophylline, or zileuton
Step 4	*< 5 years*: Medium-dose ICS + either LABA or montelukast *≥ 5 years*: Medium-dose ICS + LABA	*5–11 years*: Medium-dose ICS + either LTRA or theophylline *≥ 12 years*: Medium-dose ICS + LRTA, theophylline, or zileuton
Step 5	*< 5 years*: High-dose ICS + either LABA or montelukast *5–11 years*: High-dose ICS + LABA *≥ 12 years*: High-dose ICS + LABA *AND* consider omalizumab for patients who have allergies	*5–11 years*: High-dose ICS + either LRTA or theophylline
Step 6	*< 5 years*: High-dose ICS + oral systemic corticosteroids + either LABA or montelukast *5–11 years*: High-dose ICS + LABA + oral systemic corticosteroids *≥ 12 years*: High-dose ICS + LABA + oral systemic corticosteroids *AND* consider omalizumab for patients who have allergies	*5–11 years*: High-dose ICS + either LRTA or theophylline + oral systemic corticosteroids

Note: The stepwise approach is meant to assist in, not replace, clinical decision-making. If clear benefit is not observed within 4–6 weeks when patient technique and adherence are satisfactory, consider adjusting therapy and/or consider alternative diagnoses. Before increasing a step, review patient adherence, inhaler technique, environmental control, and comorbid conditions. When possible, step down if asthma is well controlled for at least 3 months.

ICS = inhaled corticosteroids; LABA = long-acting β-agonist; LTRA = leukotriene receptor antagonist; PEF = peak expiratory flow; PRN = as needed; SABA = short-acting β-agonist.

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

Table 7. Classifying the Severity of Asthma Exacerbations

	Signs and Symptoms	Initial PEF (or FEV_1)[a]	Clinical Course
Mild	Dyspnea only with activity (assess tachypnea in young children)	PEF ≥ 70% of predicted or personal best	▪ Usually cared for at home ▪ Prompt relief with inhaled SABA ▪ Possible short course of oral systemic corticosteroids ▪ May consider early escalation to high-dose inhaled corticosteroid
Moderate	Dyspnea interferes with or limits usual activity	PEF 40% to 69% of predicted or personal best	▪ Usually requires office or EC visit ▪ Relief from frequent inhaled SABA ▪ Oral systemic corticosteroids ▪ Some symptoms last for 1–2 days after treatment is begun
Severe	Dyspnea at rest; interferes with conversation	PEF < 40% of predicted or personal best	▪ Usually requires emergency department visit and likely hospitalization ▪ Partial relief from frequent inhaled SABA ▪ Oral systemic corticosteroids; some symptoms last for > 3 days after treatment is begun ▪ Adjunctive therapies are helpful
Life Threatening	Too dyspneic to speak; perspiring	PEF < 25% of predicted or personal best	▪ Requires emergency department hospitalization; possible ICU ▪ Minimal or no relief from frequently inhaled SABA ▪ Intravenous corticosteroids ▪ Adjunctive therapies are helpful

[a]Note that some individuals with smaller lungs in relation to their height may NORMALLY have FEV_1 < 80% and/or FEV_1/FVC < 85%. Lung function measures should be correlated with clinical assessment of asthma severity. For infants, assessment depends primarily on physical examination (use of accessory muscles, inspiratory and expiratory wheezing, paradoxical breathing, cyanosis, and a respiratory rate > 60 breaths/minute are key signs of serious distress), although objective measurements, such as oxygen saturation < 90%, also indicate serious distress.
EC = emergency center; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PEF = peak expiratory flow; SABA = short-acting β-agonist; ICU = intensive care unit.
Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

β_2-Agonists

The β_2-agonists are the most effective drugs in reversing bronchoconstriction and relaxing airway smooth muscle. Delivery of these medications directly to the airway by inhalation enhances broncho-selectivity, provides a more rapid response, and protects against triggers of bronchospasm. The SABAs—albuterol, levalbuterol, metaproterenol, terbutaline, and pirbuterol—have an onset of action within 1–5 minutes and bronchodilation that lasts 2–6 hours. Although their β_2/β_1 potency ratios vary, they are all selective for the β_2 subtype. There is little evidence that intravenous terbutaline has an added benefit for acute exacerbations compared with SABAs, corticosteroids, and ipratropium. Two of the long-acting β_2-agonists (LABAs), formoterol and salmeterol, have higher lipophilicity compared with the SABAs, which regulate the diffusion rate from the receptor (Reference 41). The LABAs are used with inhaled corticosteroids (ICS) to prevent symptoms and do not provide quick relief of symptoms. Given the frequency of use of LABAs and ICS, several products combine the two classes of medication into one delivery device.

Corticosteroids

Corticosteroids have long been employed to treat severe chronic asthma and severe exacerbations by the systemic route, but the development of aerosol formulations has allowed improved safety to extend their use in the treatment of persistent asthma. Evidence suggests that currently available therapy controls, but does not modify, the underlying disease process, and evidence supports the immediate use of systemic steroids during an exacerbation (References 1, 42–45).

Table 8. Formal Evaluation of Asthma Exacerbation Severity

	Mild	Moderate	Severe	Imminent Risk of Respiratory Arrest
Symptoms				
Breathlessness	While walking	While at rest (infant - softer, shorter cry, difficulty feeding)	While at rest (infant stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy or confused
Signs				
Respiratory rate	Increased	Increased	Often > 30/minute	
	Guide to rates of breathing in awake children:			
	Age / *Normal rate* < 2 months / < 60/minute 2–12 months / < 50/minute 1–5 years / < 40/minute 6–8 years / < 30/minute			
Use of accessory muscles	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Heart rate/ minute	< 100	100–120	> 120	Bradycardia
	Guide to normal heart rates in children:			
	Age / *Normal rate* 2–12 months / < 160/minute 1–2 years / < 120/minute 2–8 years / < 110/minute			
Pulsus paradoxus	Absent < 10 mm Hg	May be present 10–25 mm Hg	Often present > 25 mm Hg (adult) 20–40 mm Hg (child)	Absence suggests respiratory muscle fatigue
Functional Assessment				
PEF % of predicted or % of personal best	≥ 70%	Around 40% to 69% or response lasts < 2 hours	< 40%	< 25% Note: PEF testing may not be needed in very severe attacks.
Pao_2 (on air)	Normal (test not usually necessary)	≥ 60 mm Hg (test not usually necessary)	< 60 mm Hg: possible cyanosis	
and/or Pco_2	< 42 mm Hg (test not usually necessary)	< 42 mm Hg (test not usually necessary)	≥ 42 mm Hg: possible respiratory failure	
Sao_2 % (on air) at sea level	> 95% (test not usually necessary)	90% to 95% (test not usually necessary)	< 90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents.			

PEF = peak expiratory flow.

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

Methylxanthines

Methylxanthines are ineffective when aerosolized; they must therefore be administered systemically for effect. Theophylline is primarily eliminated through metabolism by the hepatic cytochrome P450 (CYP) mixed-function oxidase microsomal enzymes, primarily the CYP1A2 and CYP3A3 isozymes. The inhibition and induction of the hepatic CYP enzymes by environmental factors and drugs alter the metabolism of theophylline, necessitating a review of potential interactions. In addition, intra-patient variability in theophylline clearance is considerable; thus, serum theophylline concentrations should be monitored routinely.

Anticholinergics

Anticholinergic medications are effective bronchodilators but are not as potent as β_2-agonists. The use of ipratropium bromide during acute exacerbations in the emergency department setting is well supported by evidence; however, there is evidence against their routine use as well as their use for in-hospital care (References 46, 47).

Mast-Cell Stabilizers

The mast-cell stabilizers cromolyn and nedocromil do not produce a bronchodilatory effect and are effective only by inhalation. These medications are limited by their adverse effect profile and dosing frequency. They are thus not the first choice for childhood asthma because of their lack of efficacy and safety.

Leukotriene Modifiers

Three of the leukotriene modifiers, montelukast, zafirlukast, and zileuton, may be used as alternatives for mild persistent asthma or as adjuncts to ICS for other asthma severities. They are not indicated for treating acute episodes of asthma and must be taken regularly, even during symptom-free periods.

Immunomodulators

Subcutaneous immunotherapy with omalizumab is indicated for adolescents who have a clearly documented allergen relationship with their moderate-severe persistent asthma symptoms (Reference 48).

Other Medications

Other medications that have been suggested in the treatment of asthma include antihistamines, methotrexate, macrolides, other antibiotics, hydroxychloroquine, dapsone, gold, intravenous gamma-globulin, cyclosporine, colchicine, NSAIDs (nonsteroidal anti-inflammatory drugs), inhaled heparin, inhaled furosemide, expectorants, and magnesium sulfate. Information to recommend these therapies routinely for the long-term management and treatment of acute exacerbations is limited, but there is evidence supporting the use of magnesium sulfate only in acute severe exacerbations (References 49–53). Heliox, a mixture of helium and oxygen, has also been studied for the treatment of acute exacerbations, but the results to support their routine use as an added benefit to β_2-agonists and corticosteroids are lacking (References 54–56).

Delivery Devices

Many delivery devices are used for administering medications to manage and treat asthma. Table 12 lists several different asthma devices, their limitations, and the optimal technique to ensure the best possible delivery for various pediatric patients (Reference 1).

Monitoring Therapy

Given that asthma is a chronic inflammatory disease with episodes of acute exacerbation, the need to follow therapeutic outcomes through the assessment and monitoring of severity, control, and responsiveness is paramount. In addition to regularly scheduled follow-ups, patients should monitor their asthma control and severity and adhere to their asthma action plan. A peak flow meter is recommended for those with moderate to severe persistent asthma, as well as for those with a history of exacerbations, to regularly monitor lung function and response to treatment. If the patient is unable to use a peak flow meter, a symptom-based action plan is useful in the home management of acute exacerbations. Therapeutic outcomes must be balanced against adverse events and toxicity.

Future Therapies

Given the significant impact of asthma, advances are continuously being made to create and identify novel therapies that are effective at reducing impairment and risk as well as the underlying disease pathology. Therapies under evaluation include bronchial thermoplasty, which delivers thermal energy to the airway wall to reduce excessive airway smooth muscle; anticytokine therapies (interleukin-5, interleukin-4), which reduce inflammation; and novel steroids, referred to as "soft steroids," which are intended to produce an anti-inflammatory effect with minimal adverse effects.

Conclusions

The management of asthma involves the interplay of four essential components: (1) routine monitoring of symptoms and lung function, (2) patient education, (3) control of trigger factors and comorbid conditions, and

Table 9. Exacerbation Management

In-home and/or Office

Assess Severity

- Patients at risk of life-threatening asthma require immediate medical attention after treatment.
- Symptoms and signs suggestive of a more serious exacerbation should result in initial treatment while immediately consulting with a clinician.
- Less severe signs and symptoms can be treated initially with assessing response to therapy and taking further steps as listed below.
- If available, measure PEF.
  - 50% to 79% of predicted or personal best indicates need for quick-relief medication.
  - < 50% indicates need for immediate medical care.

Initial Treatment

Inhaled SABA: up to two treatments 20 minutes apart of 2-6 puffs by MDI or nebulizer treatments. Children may need fewer puffs.

Good Response

No wheezing or dyspnea (tachypnea - young children)

PEF ≥ 80% of predicted or personal best

- Contact clinician for follow-up instructions and further management.
- May continue inhaled SABA every 3–4 hours for 24–48 hours.
- Consider short course of oral systemic corticosteroids.

Incomplete Response

Persistent wheezing and dyspnea (tachypnea).

PEF 50% to 79% of predicted or personal best

- Add oral systemic corticosteroid.
- Continue inhaled SABA.
- Contact clinician urgently for further instruction.

Poor Response

Marked wheezing and dyspnea

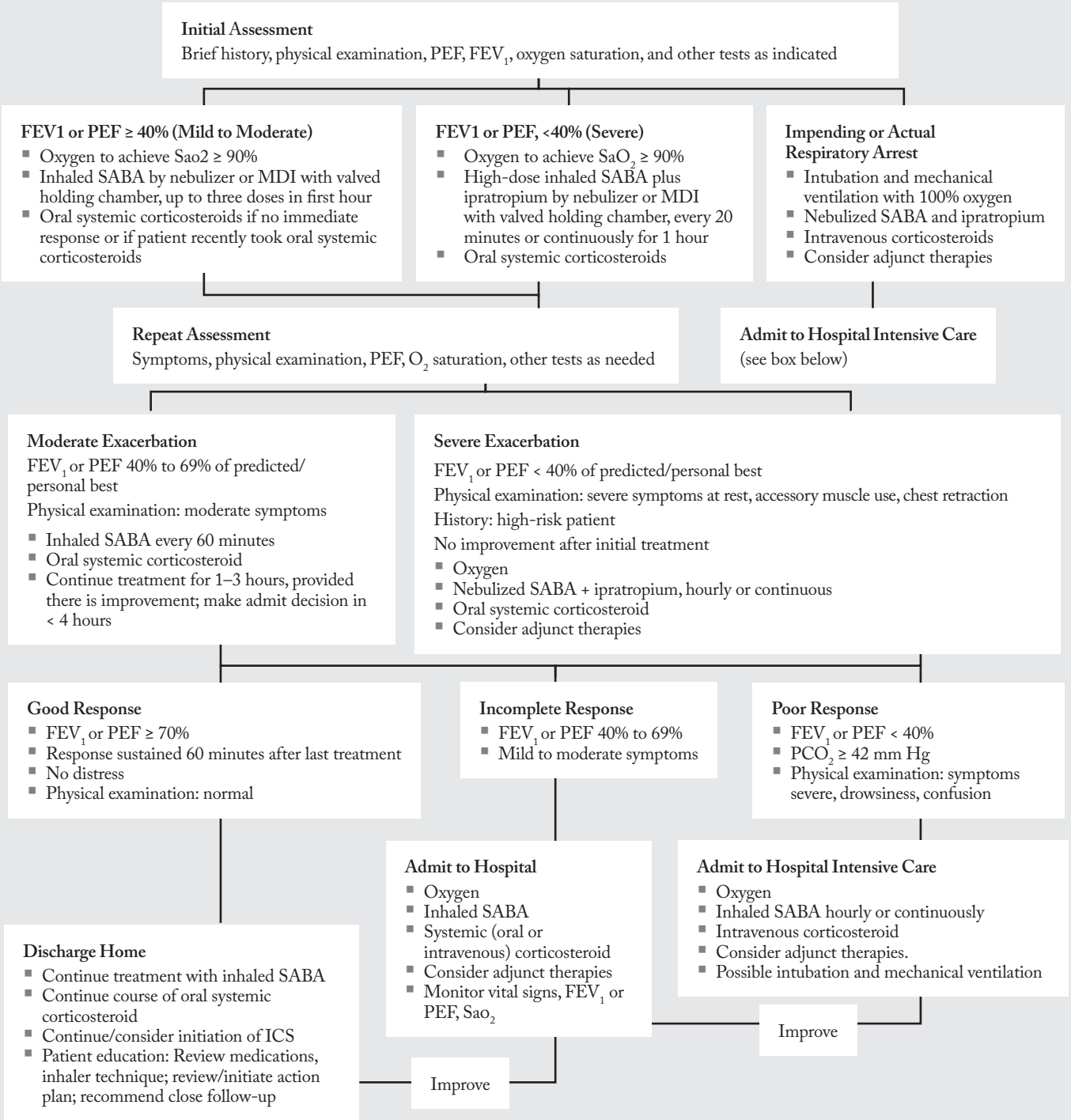
PEF < 50% of predicted or personal best

- Add oral systemic corticosteroid.
- Repeat inhaled SABA immediately.
- If distress is severe and unresponsive to initial treatment:
  - Call your clinician AND
  - Proceed to emergency department
  - Consider calling 911

(continued)

Table 9. Exacerbation Management *(continued)*

Emergency Department and Hospital



EIB = exercise-induced bronchospasm; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; MDI = metered dose inhaler; PEF = peak expiratory flow; SABA = short-acting β-agonist.

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

Table 10. Medications Used in the Treatment of Asthma

Class and Medication	Mechanism and Indication(s)	Potential Adverse Effects	Therapeutic Issues
β_2-Agonists	*Mechanism* ▪ **Bronchodilation.** Stimulation of β_2-adrenergic receptors leads to activation of adenylate cyclase and increase in cyclic adenosine monophosphate, which results in smooth muscle relaxation, producing functional antagonism of bronchoconstriction.	▪ Inhaled route, in general, causes few systemic adverse effects. ▪ Tachycardia, skeletal muscle tremor, hypokalemia, increased lactic acid, headache, hyperglycemia, prolongation of QTc interval in overdose ▪ A diminished bronchoprotective effect may occur within 1 week of chronic therapy. Clinical significance has not been established.	
SABAs *Inhaled:* Albuterol Levalbuterol Pirbuterol	*Indications* ▪ Relief of acute symptoms; quick-relief medication ▪ Preventive treatment for EIB before exercise	▪ In addition to above, restlessness, irritability, nervousness, and insomnia	▪ Drugs of choice for acute bronchospasm. Inhaled route has faster onset and fewer adverse effects and is more effective than systemic routes. The less β_2-selective agents (isoproterenol, metaproterenol, isoetharine, and epinephrine) are not recommended because of their potential for excessive cardiac stimulation, especially in high doses. ▪ Regularly scheduled daily use is not recommended. ▪ Regular use > 2 days/week for symptom control (not prevention of EIB), increasing use, or lack of expected effect indicates inadequate asthma control and need for anti-inflammatory medication.
LABAs *Inhaled:* Formoterol Salmeterol	*Indications* ▪ Long-term prevention of symptoms, added to ICS ▪ Prevention of EIB ▪ *Not to be used to treat acute symptoms or exacerbations*	▪ In addition to above, potential risk of uncommon, severe, life-threatening, or fatal exacerbation (black box warning for asthma-related deaths)	▪ Not to be used to treat acute symptoms or exacerbations ▪ Should not be used as monotherapy for long-term control of asthma or as anti-inflammatory therapy. ▪ May provide more effective symptom control when added to standard doses of ICS compared with increasing the ICS dosage ▪ Clinical significance of potentially developing tolerance is uncertain because studies show symptom control and bronchodilation are maintained.
Oral: Albuterol, sustained release			▪ Inhaled route is preferred because LABAs are longer acting and have fewer adverse effects than oral sustained-release agents. Oral agents have not been adequately studied as adjunctive therapy with ICS.
Corticosteroids (glucocorticoids)	*Mechanism* ▪ **Anti-inflammatory.** Block late reaction to allergen and reduce airway hyperresponsiveness. Inhibit cytokine production, adhesion protein activation, and inflammatory cell migration and activation. ▪ Reverse β_2-receptor down-regulation. Inhibit microvascular leakage		

(continued)

Table 10. Medications Used in the Treatment of Asthma *(continued)*

Class and Medication	Mechanism and Indication(s)	Potential Adverse Effects	Therapeutic Issues
Inhaled (ICS): Beclomethasone dipropionate Budesonide Ciclesonide Flunisolide Fluticasone propionate Mometasone furoate Triamcinolone acetonide	*Indications* ▪ Long-term prevention of symptoms; suppression, control, and reversal of inflammation ▪ Reduce need for oral corticosteroid	▪ Cough, dysphonia, oral thrush (candidiasis) ▪ In high doses, systemic effects (e.g., adrenal suppression, osteoporosis, skin thinning, and easy bruising) may occur, although studies are not conclusive, and clinical significance of these effects has not been established. ▪ In low to medium doses, suppression of growth velocity has been observed in children, but this effect may be transient, and the clinical significance has not been established.	▪ Spacer/holding chamber devices with non–breath-activated MDIs and mouth washing after inhalation decrease local adverse effects. ▪ The risks of uncontrolled asthma should be weighed against the limited risks of ICS therapy. The potential but small risk of adverse events is well balanced by their efficacy. ▪ Dexamethasone is not included as an ICS for long-term control because it is highly absorbed and has long-term suppressive adverse effects.
Systemic: Methylprednisolone Prednisolone Prednisone	*Indications* ▪ For short-term (3–10 days) "burst" to gain prompt control of inadequately controlled persistent asthma ▪ For moderate or severe exacerbations to prevent progression of exacerbation, reverse inflammation, speed recovery, and reduce rate of relapse ▪ For long-term prevention of symptoms in severe persistent asthma: suppression, control, and reversal of inflammation	▪ *Short-term use*: reversible abnormalities in glucose metabolism, increased appetite, fluid retention, weight gain, facial flushing, mood alteration, hypertension, peptic ulcer, and rarely aseptic necrosis ▪ *Long-term use*: adrenal axis suppression, growth suppression, dermal thinning, hypertension, diabetes, Cushing syndrome, cataracts, muscle weakness, and impaired immune function ▪ Consideration should be given to coexisting conditions that could be worsened by systemic corticosteroids, such as herpes virus infections, varicella, tuberculosis, hypertension, peptic ulcer, diabetes mellitus, osteoporosis, and *Strongyloides.*	▪ Other systemic corticosteroids such as hydrocortisone and dexamethasone given in equipotent daily doses are likely to be as effective as prednisolone. ▪ Short-term therapy should continue until patient's symptoms resolve. This usually requires 3–10 days but may require longer. Action may begin within 1 hour. ▪ Use at lowest effective dose. For long-term use, alternate-day morning dosing produces the least toxicity. ▪ There is no evidence that tapering the dose after improvement is useful in preventing a relapse in asthma exacerbations.
Methylxanthines Theophylline, sustained-release tablets and capsules	*Mechanism* ▪ **Bronchodilation.** Smooth muscle relaxation from phosphodiesterase inhibition and possibly adenosine antagonism ▪ May affect eosinophilic infiltration into bronchial mucosa as well as decreases in T-lymphocyte numbers in epithelium ▪ Increases diaphragm contractility and mucociliary clearance *Indication* ▪ Long-term control and prevention of symptoms in mild persistent asthma or as adjunctive with ICS, in moderate or persistent asthma ▪ NHLBI guidelines (2007) do not recommend oral theophylline as a long-term control medication for asthma in children ≤ 5 years.	▪ Dose-related acute toxicities include tachycardia, nausea and vomiting, tachyarrhythmias (SVTs), central nervous system stimulation, headache, seizures, hematemesis, hyperglycemia, and hypokalemia. ▪ Adverse effects at usual therapeutic doses include insomnia, gastric upset, aggravation of ulcer or reflux, and increase in hyperactivity in some children.	▪ Maintain steady-state serum concentrations 5–15 mcg/mL. Routine serum concentration monitoring is essential because of significant toxicities, narrow therapeutic range, and individual differences in metabolic clearance. Absorption and metabolism may be affected by several factors that can produce significant changes in steady-state serum theophylline concentrations. ▪ Patients should be told to discontinue if they experience toxicity. ▪ Not generally recommended for exacerbations. There is minimal evidence for added benefit to optimal doses of SABA. ▪ Serum concentration monitoring is mandatory.

Class and Medication	Mechanism and Indication(s)	Potential Adverse Effects	Therapeutic Issues
Anticholinergics Ipratropium bromide	*Mechanism* ▪ **Bronchodilation.** Competitive inhibition of muscarinic cholinergic receptors ▪ Reduces intrinsic vagal tone of the airways. May block reflex bronchoconstriction secondary to irritants or to reflux esophagitis ▪ May decrease mucous gland secretion *Indication* ▪ Relief of acute bronchospasm	▪ Drying of mouth and respiratory secretions, increased wheezing in some individuals, blurred vision if sprayed in eyes. If used in the emergency department, produces less cardiac stimulation than SABAs	▪ Reverses only cholinergically mediated bronchospasm; does not modify reaction to antigen. Does not block EIB ▪ Several doses of ipratropium in the emergency department provide additive effects to SABA. ▪ May be alternative for patients who do not tolerate SABAs ▪ Treatment of choice for bronchospasm because of β-blocker medication ▪ Has not proven efficacious as long-term control therapy for asthma
Mast-cell stabilizers Cromolyn sodium Nedocromil	*Mechanism* ▪ **Anti-inflammatory.** Blocks *early* and late reaction to allergen. Interferes with chloride channel function ▪ Stabilizes mast-cell membranes and inhibits activation and release of mediators from eosinophils and epithelial cells ▪ Inhibits acute response to exercise, cold dry air, and SO_2. *Indications* ▪ Long-term prevention of symptoms in mild persistent asthma; may modify inflammation ▪ Preventive treatment before exposure to exercise or known allergen	▪ Cough and irritation ▪ 15% to 20% of patients experience an unpleasant taste from nedocromil.	▪ Therapeutic response to cromolyn and nedocromil often occurs within 2 weeks, but a 4- to 6-week trial may be needed to determine maximal benefit. ▪ Dose of cromolyn by MDI may be inadequate to affect airway hyperresponsiveness. Nebulizer delivery may be preferred for some patients. ▪ Safety is the primary advantage of these agents.
LTRAs	*Mechanism* ▪ Selective competitive inhibitor of CysLT1 receptor, a potent constrictor of bronchial smooth muscle		▪ May attenuate EIB in some patients, but less effective than ICS therapy
Montelukast tablets and granules	*Indication* ▪ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥1 year. May also be used with ICS as combination therapy in moderate persistent asthma	▪ Postmarketing reports of behavioral changes (e.g., agitation, aggression, depression, insomnia, tremor) have been noted in pediatric patients. ▪ Rare cases of Churg-Strauss have occurred, but the association is unclear.	▪ A flat dose-response curve, without further benefit, if dose is increased beyond recommendations

(continued)

Table 10. Medications Used in the Treatment of Asthma *(continued)*

Class and Medication	Mechanism and Indication(s)	Potential Adverse Effects	Therapeutic Issues
Zafirlukast tablets	*Indication* ▪ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥7 years. ▪ May also be used with ICS as combination therapy in moderate persistent asthma.	▪ Postmarketing surveillance has reported cases of reversible hepatitis and, rarely, irreversible hepatic failure resulting in death and liver transplantation.	▪ Administration with meals decreases bioavailability; take at least 1 hour before or 2 hours after meals. ▪ Zafirlukast is a microsomal cytochrome P450 enzyme inhibitor that can inhibit the metabolism of warfarin. INRs should be monitored during coadministration. ▪ Patients should be warned to discontinue use if they experience signs and symptoms of liver dysfunction (right upper quadrant pain, pruritus, lethargy, jaundice, nausea), and patients' ALTs should be monitored.
5-Lipoxygenase inhibitor	*Mechanism* ▪ Inhibits the production of leukotrienes from arachidonic acid, both LTB4 and the cysteinyl leukotrienes		
Zileuton tablets	*Indication* ▪ Long-term control and prevention of symptoms in mild persistent asthma for patients ≥ 12 years ▪ May be used with ICS as combination therapy in moderate persistent asthma in patients ≥ 12 years	▪ Elevation of liver enzymes has been reported. Limited case reports of reversible hepatitis and hyperbilirubinemia	▪ Zileuton is microsomal cytochrome P450 enzyme inhibitor that can inhibit the metabolism of warfarin and theophylline. Doses of these drugs should be monitored accordingly. ▪ Monitor hepatic enzymes (ALT).
Immunomodulators Omalizumab (anti-IgE) for subcutaneous use	*Mechanism* ▪ Binds to circulating IgE, preventing it from binding to the high-affinity (FcεRI) receptors on basophils and mast cells ▪ Decreases mast-cell mediator release from allergen exposure ▪ Decreases the number of FcεRIs in basophils and submucosal cells *Indication* ▪ Long-term control and prevention of symptoms in adults (≥ 12 years old) who have moderate or severe persistent allergic asthma inadequately controlled with ICS	▪ Pain and bruising of injection sites has been reported in 5% to 20% of patients. ▪ Anaphylaxis has been reported in 0.2% of treated patients. ▪ Malignant neoplasms were reported in 0.5% of patients compared with 0.2% receiving placebo; relationship to drug is unclear	▪ Monitor patients after injection. Be prepared and equipped to identify and treat anaphylaxis that may occur. ▪ The dose is administered either every 2 or 4 weeks, depending on the patient's body weight and IgE level before therapy. ▪ A maximum of 150 mg can be administered in one injection. ▪ Needs to be stored under refrigeration at 2°C–8°C ▪ Whether patients will develop significant antibody titers to the drug with long-term administration is unknown.

ALT = alanine aminotransferase; EIB = exercise-induced bronchospasm; ICS = inhaled corticosteroids; IgE = immunoglobulin E; INR = international normalized ratio; LABA = long-acting β_2-agonist; LRTA = leukotriene receptor antagonist; LTB4 = leukotriene B4; MDI = metered dose inhaler; NHLBI = National Heart, Lung, and Blood Institute; SABA = short-acting β_2-agonist; SVT = supraventricular tachyarrhythmia.

Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

Table 11. Asthma Medications and Dosing Based on Age Category

Medication	< 5 years			5–11 years			≥ 12 years		
Inhaled corticosteroids	**Low Daily Dose**	**Medium Daily Dose**	**High Daily Dose**	**Low Daily Dose**	**Medium Daily Dose**	**High Daily Dose**	**Low Daily Dose**	**Medium Daily Dose**	**High Daily Dose**
Beclomethasone HFA 40 or 80 mcg/puff	N/A	N/A	N/A	80–160 mcg	> 160–320 mcg	> 320 mcg	80–240 mcg	> 240–480 mcg	>480 mcg
Budesonide DPI 90, 180, 200 mcg/inhalation	N/A	N/A	N/A	180–400 mcg	> 400–800 mcg	> 800 mcg	180–600 mcg	> 600–1200 mcg	>1200 mcg
Budesonide inhaled Inhalation suspension	0.25–0.5 mg	> 0.5–1 mg	> 1 mg	0.5 mg	1 mg	2 mg	N/A	N/A	N/A
Flunisolide 250 mcg/puff	N/A	N/A	N/A	500–750 mcg	1000–1250 mcg	> 1250 mcg	500–1000 mcg	> 1000–2000 mcg	>2000 mcg
Flunisolide HFA 80 mcg/puff	N/A	N/A	N/A	160 mcg	320 mcg	≥ 640 mcg	320 mcg	> 320–640 mcg	>640 mcg
Fluticasone HFA/MDI 44, 110, 220 mcg/puff	176 mcg	> 176–352 mcg	> 352 mcg	88–176 mcg	> 352 mcg	> 352 mcg	88–264 mcg	> 264–440 mcg	>440 mcg
Fluticasone DPI 50, 100, 250 mcg/inhalation	N/A	N/A	N/A	100–200 mcg	> 200–400 mcg	> 400 mcg	100–300 mcg	> 300–500 mcg	>500 mcg
Mometasone DPI 100, 200 mcg/inhalation	N/A	N/A	N/A	*100 mcg*	*100 mcg*	*100 mcg*	200 mcg	400 mcg	>400 mcg
Triamcinolone acetonide 75 mcg/puff	N/A	N/A	N/A	300–600 mcg	> 600–900 mcg	> 900 mcg	300–750 mcg	> 750–1500 mcg	>1500 mcg
Systemic corticosteroids									
Methylprednisolone	0.25–2 mg/kg daily or every other day			0.25–2 mg/kg daily or every other day			7.5–60 mg/day or every other day		
Prednisolone Prednisone	Short-course "burst": 1–2 mg/kg/day, max 60 mg for 3–10 days			Short-course "burst": 1–2 mg/kg/day, max 60 mg for 3–10 days			Short-course "burst": 40–60 mg per day as a single or two divided doses for 3–10 days		

(continued)

Table 11. Asthma Medications and Dosing Based on Age Category *(continued)*

Medication	< 5 years	5–11 years	≥ 12 years
Short-acting β-agonists			
Albuterol HFA 90 mcg/puff	2 puffs q4–6h PRN	2 puffs q4–6h PRN	2 puffs q4–6h PRN
Albuterol nebulizer 0.63 mg/3 mL 1.25 mg/3 mL 2.5 mg/3 mL 5 mg/mL (0.5%)	0.63–2.5 mg q4–6h PRN	1.25–5 mg q4–8h PRN	1.25–5 mg q4–8h PRN
Levalbuterol HFA 45 mcg/puff	N/A	2 puffs q4–6h PRN	2 puffs q4–6h PRN
Levalbuterol nebulizer 0.31 mg/3 mL 0.63 mg/3 mL 1.25 mg/0.5 mL 1.25 mg/3 mL	0.31–1.25 mg q4–6h PRN	0.31–0.63 mg q8h PRN	0.63–1.25 mg q8h PRN
Pirbuterol Autohaler 200 mcg/puff	N/A	N/A	2 puffs q4–6h PRN
Long-acting β-agonists			
Salmeterol DPI DPI 50 mcg/blister	N/A	1 blister q12h	1 blister q12h
Formoterol DPI DPI 12-mcg/capsule	N/A	1 capsule q12h	1 capsule q12h

Medication	< 5 years	5–11 years	≥ 12 years
Combined medication			
Fluticasone/salmeterol DPI 100 mcg/50 mcg (≥ 5 years) 250 mcg/50 mcg (≥ 12 years) 500 mcg/50 mcg (≥ 12 years)	N/A	1 inhalation bid	1 inhalation bid
Fluticasone/salmeterol HFA 45 mcg/21 mcg (≥ 12 years) 115 mcg/21 mcg (≥ 12 years) 230 mcg/21 mcg (≥ 12 years)	N/A	N/A	1 inhalation bid
Budesonide/formoterol HFA/MDI 80 mcg/4.5 mcg (≥ 5 years) 160 mcg/4.5 mcg (≥ 12 years)	N/A	2 puffs bid	2 puffs bid
Mometasone/formoterol HFA/MDI 100 mcg/5 mcg (≥ 12 years) 200 mcg/5 mcg (≥ 12 years)	N/A	N/A	2 puffs bid
Anticholinergics			
Ipratropium HFA 17 mcg/puff	N/A	*1 or 2 puffs q6h*	2 or 3 puffs q6h
Ipratropium nebulizer 0.25 mg/mL	*0.125–0.25 mg q8h*	*0.25 mg q6h*	0.25 mg q6h
Ipratropium/albuterol nebulizer 0.5–2.5 mg/3 mL	N/A	N/A	3 mL q4–6h
Cromolyn/nedocromil			
Cromolyn MDI 0.8 mg/puff	N/A	2 puffs qid	2 puffs qid
Cromolyn nebulizer 20 mg/ampule	1 ampule qid (≥ 2 years)	1 ampule qid	1 ampule qid
Nedocromil MDI 1.75 mg/puff	N/A	2 puffs qid	2 puffs qid

(continued)

Table 11. Asthma Medications and Dosing Based on Age Category *(continued)*

Medication	< 5 years	5–11 years	≥ 12 years
Leukotriene modifiers			
Leukotriene receptor antagonists			
Montelukast 4 mg chew tablet (≥ 1 year) 4 mg packet (≥ 1 year) 5 mg chew tablet (> 5 years) 10 mg tablet (≥ 12 years)	4 mg qhs (1–5 years)	5 mg qhs (6–14 years)	10 mg (≥ 15 years)
Zafirlukast 10-mg tablet (5–11 years) 20-mg tablet (≥ 12 years)	N/A	10 mg bid (5–11 years)	40 mg/day (20-mg tablet bid)
5-Lipoxygenase inhibitor			
Zileuton 600-mg tablet (≥ 12 years)	N/A	N/A	2400 mg/day (give tablets qid)
Methylxanthines			
Theophylline	Starting dose 10 mg/kg/day; usual maximum 16 mg/kg/day (≥ 1 year)	Starting dose 10 mg/kg/day; usual maximum 16 mg/kg/day	Starting dose 10 mg/kg/day; up to 300 mg maximum, usual maximum 800 mg/day
Immunomodulators			
Omalizumab subcutaneous injection 150 mg/1.2 mL	N/A	N/A	150–375 mg SC q 2–4 weeks, depending on weight and serum IgE level

bid = twice daily; DPI = dry powder inhaler; h = hours; HFA = hydrofluoroalkane; IgE = immunoglobulin E; MDI = metered dose inhaler; N/A = not applicable; PRN = as needed; q = every; qid = four times/day; s = second; SC = subcutaneously.

Adapted from FDA-approved product labeling; Taketomo CK, Hodding JH, Kraus DM. Pediatric & Neonatal Dosage Handbook, 18th ed. Hudson, OH: Lexi-Comp, 2011; and the National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (References 1, 40). Dosages that are italicized are based on data from clinical trials that support use in patients beyond the FDA-approved labeling.

Table 12. Delivery Devices

Device/Drugs	Population	Optimal Technique	Therapeutic Issues
MDI β_2-Agonists Corticosteroids Cromolyn sodium Anticholinergics	≥ 5 years old (< 5 with spacer or VHC mask)	Actuation during a slow (3–5 seconds), deep inhalation, followed by a 10-second breath hold	Slow inhalation and coordination of actuation during inhalation may be difficult, particularly in young children. Patients may incorrectly stop inhalation at actuation. Deposition of 50% to 80% of actuated dose in oropharynx. Mouth washing and spitting is effective in reducing the amount of drug swallowed and absorbed systemically.
Breath-actuated MDI β_2-Agonists	≥ 5 years old	Tight seal around mouthpiece and slightly more rapid inhalation than standard MDI, followed by a 10-second breath hold	May be useful for patients unable to coordinate inhalation and actuation. Patients may incorrectly stop inhalation at actuation. Cannot be used with spacer/VHC devices
DPI β_2-Agonists Corticosteroids Anticholinergics	≥ 4 years old	Rapid (1 or 2 seconds), deep inhalation. Minimally effective inspiratory flow is device-dependent. Most children < 4 years do not generate sufficient inspiratory flow to activate the inhaler.	Dose is lost if patient exhales through device after actuating. Delivery may be greater or lesser than MDI, depending on device and technique. Rapid inhalation promotes greater deposition in larger central airways. Mouth washing and spitting is effective in reducing amount of drug swallowed and absorbed.
Spacer or VHC	≥ 4 years old	Slow (3–5 seconds), deep inhalation, followed by 10-second breath hold immediately after each actuation.	Indicated for patients who have difficulty performing adequate MDI technique. The VHC improves lung delivery and response in patients who have poor MDI technique. Face mask allows MDIs to be used with small children. However, use of a face mask reduces delivery to lungs by 50%.
	< 4 years old VHC with face mask	If face mask is used, it should have a tight fit and allow 3–5 inhalations per actuation.	Spacers and/or VHCs decrease oropharyngeal deposition. Rinse plastic VHCs once a month with dilute household dishwashing detergent.
Nebulizer β_2-Agonists Corticosteroids Cromolyn sodium Anticholinergics	Patients of any age who cannot use MDI with VHC and face mask	Slow tidal breathing with occasional deep breaths. Tightly fitting face mask for those unable to use mouthpiece. Using the "blow-by" technique (holding the mask or open tube near the infant's nose and mouth) is not appropriate.	Less dependent on patient's coordination and cooperation May be expensive; time-consuming Use of a face mask reduces delivery to lungs by 50%. Nebulizers are as effective as MDIs plus VHCs for delivering bronchodilators in mild to moderate exacerbations. Potential for bacterial infections if not cleaned properly

DPI = dry powder inhaler; MDI = metered dose inhaler; VHC = valved holding chamber.
Adapted from National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program, Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, Full Report. Washington, DC: U.S. Department of Health and Human Services, National Institutes of Health, 2007 (Reference 1).

(4) pharmacologic therapy. The primary goal of asthma management is centered on the principle of asthma control through the reduction of risk and impairment. Effective asthma management, which varies on the basis of patient age, requires a preventive approach, with routine visits to assess symptoms, monitor pulmonary function, adjust medications, and ensure education is provided to allow self-management and control. Efforts should be made to identify and address environmental triggers and comorbid conditions that affect asthma management. Pharmacologic therapy varies according to asthma severity and asthma control through a stepwise approach, in which the class and number of medications, dosing, and frequency of administration are increased when necessary and reduced when possible. Pharmacists play an important role in educating and ensuring understanding of pharmacologic and nonpharmacologic means for the effective management of asthma.

Asthma is the most common chronic disease in childhood, and despite the long course of its history, its etiology is still not clearly understood. The burden that this chronic inflammatory disease places on those whom it affects and the amount of resources is significant. Until we have a greater understanding of its cause and identify a means of preventing the development of this disease, pharmacologic and nonpharmacologic therapy to control asthma through the reduction of risk and impairment is of extreme importance.

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CHAPTER 15

Cystic Fibrosis

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Learning Objectives

1. Describe the incidence and inheritance pattern of cystic fibrosis (CF).
2. Recognize common signs and symptoms of CF, including its initial presentation and multiorgan system effects throughout life.
3. Identify and apply CF-specific pharmacokinetic differences in the selection of antimicrobial therapy.
4. Determine appropriate chronic and acute exacerbation therapy and accompanying monitoring parameters to meet efficacy and safety needs of patients with CF.
5. Discuss the role of a pharmacist as part of the CF interdisciplinary care team and community.

Abbreviations in This Chapter

BMI	Body mass index
CF	Cystic fibrosis
CFRD	CF-related diabetes
CFTR	CF-transmembrane conductance regulator
DIOS	Distal intestinal obstruction syndrome
FEV_1	Percent predicted forced expiratory volume in 1 second
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
MRSA	Methicillin-resistant *Staphylococcus aureus*
PA	*Pseudomonas aeruginosa*
PERT	Pancreatic enzyme replacement therapy
SIBO	Small intestinal bacterial overgrowth

Introduction

Cystic fibrosis (CF) is a genetic, autosomal-recessive, multiorgan disease affecting more than 30,000 and 70,000 individuals in the United States and worldwide, respectively (Reference 1). Cystic fibrosis is the most common inherited disease in the white population worldwide. This disease has an incidence of 1 in 3500 births in the United States and an overall incidence as high as about 1 in 1300 in European countries such as Ireland (References 2, 3). Cystic fibrosis also affects a variety of races and ethnicities, with the greatest incidence within the white population (more than 90% of patients with CF in the United States) and a lower incidence among Hispanic (1 in 1900), Asian (1 in 32,000), and African American (1 in 15,000) populations (Reference 3). Without a current cure, CF continues to be a life-shortening, genetic disease most commonly affecting the pulmonary and gastrointestinal (GI) systems with additional effects on the reproductive system, bone, and sudoriferous (sweat) glands. Because of the technological advances of airway clearance, paired with the discovery of effective drug therapies, the median life span of patients with CF has extended from 10 years in 1960 to 37.4 years in 2010 (References 1, 2). Given the multifaceted aspect of CF as a disease, there is a need for an interdisciplinary approach to patient care because of complex drug therapy regimens.

Pathophysiology and Genetics of CF

Cystic fibrosis is the result of a mutation of a single gene in the long arm of chromosome 7. This mutation affects the CF-transmembrane conductance regulator (CFTR), a membrane ion channel in secretory epithelial cells notably found in airway lumens and the pancreatic duct. The CFTR is mediated by cyclic adenosine 3′,5′-monophosphate (cAMP). In an individual without CF, cAMP activates the transport of chloride (Cl^-) from the cell by CFTR, which corresponds with sodium (Na^+) and water efflux. In individuals with CF, Cl^- and Na^+ movement is significantly decreased or absent, resulting in decreased secretion of Cl^- paired with increased Na^+ retention and water retention in the submucosa (Figure 1). The subsequent loss of volume in epithelial secretions causes them to be thick and viscous, decreasing mucociliary function and causing mucus-associated obstruction and inflammation. This dysfunction usually affects pulmonary epithelia; however, depending on a patient's phenotype, the patient may also exhibit effects to the pancreatic and hepatobiliary ducts as well as to the microvilli of the GI tract (Reference 3).

The five main classes of mutations associated with CFTR include more than 1,200 known mutations. The CFTR mutations are classified by the mechanism from which they affect CFTR function (Table 1 and Figure 2). Class I mutations affect the synthesis of CFTR,

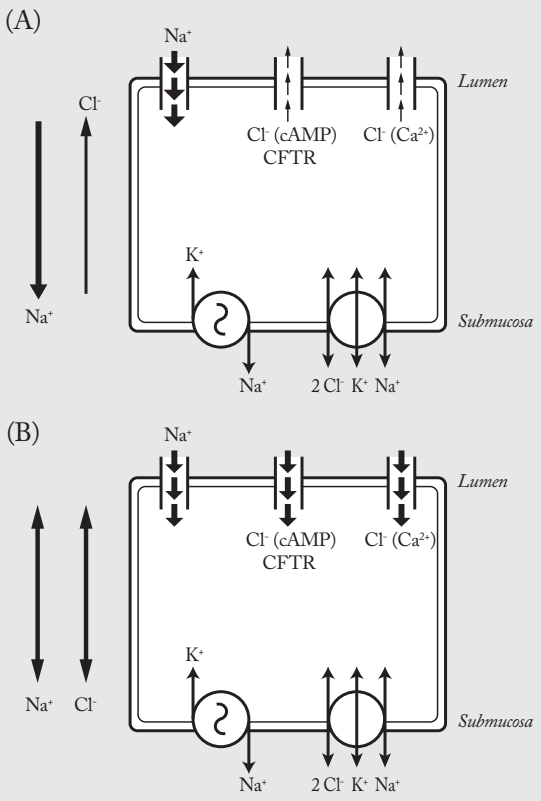


Figure 1. Electrolyte movement in epithelial cell in (A) individual with CF and (B) individual without CF.

Ca^{2+} = calcium; cAMP = cyclic adenosine monophosphate; CF = cystic fibrosis; CFTR = CF-transmembrane conductance regulator; Cl^- = chloride; K^+ = potassium; Na^+ = sodium.

whereas class II mutations affect the location of CFTR from the apical membrane surface. F508del, a class II mutation, is the most common mutation within the CF population, accounting for almost 70% of mutation alleles in white patients with CF. Class III and IV mutations affect the function of CFTR, specifically the regulation of CFTR function in response to cAMP and Cl^- transport, respectively. Class V mutations, also recognized as "nonsense" mutations, affect the amount of functional CFTR produced (References 3, 4).

Other ion channels influence the flux of fluid and ions as part of CF and may also present with dysfunction, including the ORCC (outwardly rectifying Cl^- channel) and the ENaC (epithelial sodium channel) (References 5–7). Like CFTR, these channels are potential therapeutic targets for future CF therapies.

The phenotype of CF disease varies on the basis of genotype combination (e.g., F508del homozygotes vs. F508del/R117H); however, phenotypes can also be heterogeneous between siblings with identical mutations (Reference 8). Thus, it is evident that other genetic factors and environmental factors affect phenotype in patients with CF (References 3, 4). Newborn genetic screening has now made it possible to detect CF at a much earlier age than the historical phenotypic-dependent screening and presentation of CF-related symptoms at a later age. The use of sweat tests, which measure the dermal excretion of Cl^-, and advanced DNA analysis, have also advanced the ability to confirm diagnosis and identify specific genotype, respectively (Reference 9). Prenatal

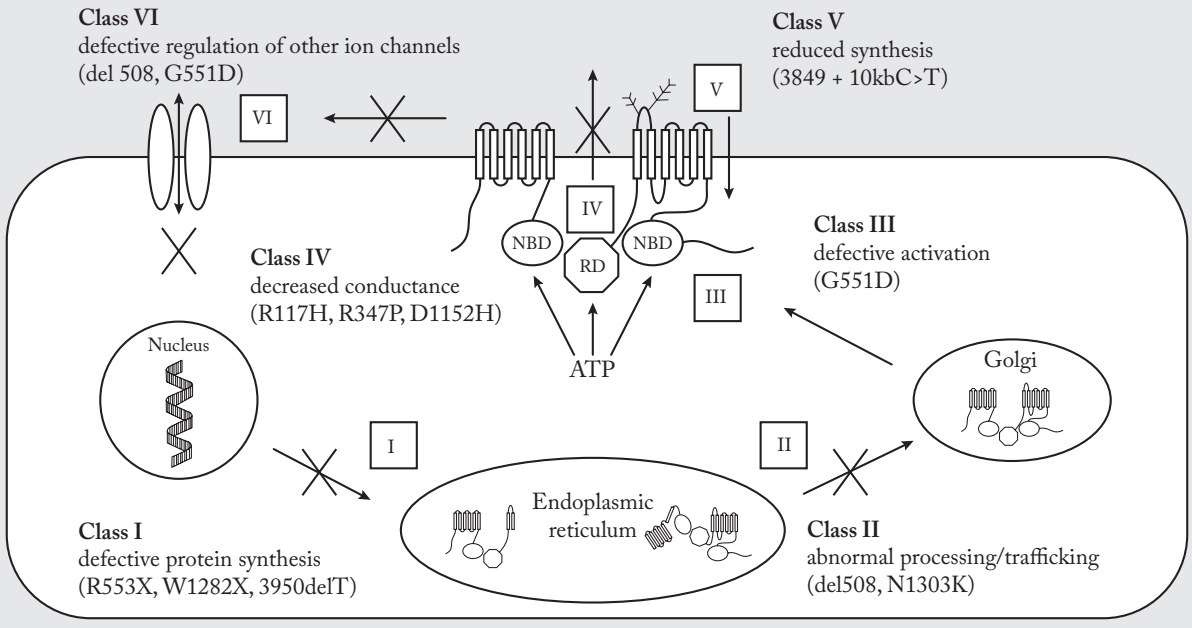


Figure 2. CFTR mutation classes.

Reprinted with permission from Witt H. Gut 2003;52(suppl II):ii31–ii41 (Reference 5).
CFTR = CF-transmembrane conductance regulator.

screening can include CF carrier status testing of parents as well as fetal testing when both parents are carriers. Fetal testing would involve chorionic villus sampling through amniocentesis, where CF gene mutations in the DNA from chorionic villus cells can be identified early in pregnancy (i.e., 11–14 weeks' gestation) (Reference 10).

Pulmonary Disease in CF

Physical Manifestation

The accumulation of thick, viscous pulmonary secretions (known as airway surface liquid) results in poor mucociliary clearance of debris and mucus by respiratory cilia. Consequently, the dehydrated nature of the airway surface liquid and mucus accumulation result in the obstruction of small and large airways. This obstruction leads to air trapping, bronchiectasis, and atelectasis. Bacteria and other foreign particles remain in the airways, leading to colonization and subsequent infection (e.g., bronchopneumonia) and inflammation. Because of the continued obstruction and inflammatory state, hyper-inflammation and dilation of airspaces are often noted in diagnostic imaging. Hemoptysis is also commonly noted in patients with CF, especially as part of pulmonary exacerbations, ranging from streaking in the sputum to massive hemoptysis. Other complications include pneumothorax, occurring in about 1 in 167 patients per year (Reference 12).

Patients with CF have distinct phenotypes of their disease, ranging from mild disease with few acute exacerbations to moderate or severe disease requiring more frequent hospitalization and acute treatment (Reference 12). In addition, patients can be stable for years and then experience a rapid loss of pulmonary function during a relatively short period. With each pulmonary infection and resulting inflammation, pulmonary function is decreased, which is commonly termed the *vicious cycle* of CF pulmonary disease (Figure 3). Percent predicted forced expiratory volume in 1 second (FEV_1) is considered a strong predictor of survival and pulmonary function in patients with CF. Studies have shown that loss of FEV_1 is greatest during adolescence when a nadir of adherence to airway clearance and drug therapy occurs, with an overall average loss of FEV_1 of between 1 and 3 FEV_1 points per year (Reference 13).

Often, the lungs of individuals with CF are colonized with gram-positive (e.g., *Staphylococcus aureus*) and/or gram-negative (e.g., *Pseudomonas aeruginosa* [PA]) pathogens in childhood (References 3, 12, 13). Pulmonary colonization and/or infection by other microbes are also noted, which can vary with factors such as age, geographic location, and exposure to pathogens (e.g., hospitalization) (References 3, 14).

Therapies for Pulmonary Disease in CF

Airway Clearance

The increased viscosity of the mucus of patients with CF and the subsequent obstruction and even mucus plugging dictate the use of physiotherapy to help loosen this mucus and help with expectoration. First approaches include chest percussion and postural drainage by positioning of the patient in multiple positions to help drain the mucus from the various lobes of the lung while cupping the hands and percussing the chest. This procedure should be done at least two or three times/day and requires about 30 minutes to complete. Because this is very difficult to do given the considerable requirement for caregiver time to manually provide physiotherapy, mechanical devices have been developed to facilitate this procedure. Chest therapy vests have been developed that use a fitted vest and pneumatic

Table 1. CFTR Mutation Classification, Effect, and Genotype Example (References 3, 4)

Mutation Class	Effect on CFTR	Common Genotype Example
I	Premature termination of production, resulting in decreased or no functional CFTR Cl^- channels	G542X
II	Defective processing of CFTR; CFTR does not reach the apical membrane surface for function	F508del[a]
III	CFTR reaches membrane surface but does not respond to cAMP stimulation resulting in defective regulation	G551D
IV	CFTR reaches membrane surface, but Cl^- transport is defective.	R117H
V	Synthesis of functional CFTR is reduced, resulting in a small amount of functional CFTR to the membrane surface.	3,849 + 10 kb C→T

[a]Most common CF mutation.
cAMP = cyclic adenosine monophosphate; CF = cystic fibrosis; CFTR = CF-transmembrane conductance regulator; Cl^- = chloride.

pressure to automate the process and help improve adherence and benefit to the patient. This type of therapy continues today, including the use of physical exercise and other devices that aid in mucus clearance to help maintain airway clearance and prevent clinical deterioration (Reference 15).

Pharmacotherapy

Treatment Guidelines

In the past 5 years, a concerted effort has been made by the Cystic Fibrosis Foundation to help establish guidelines for the treatment of both chronic therapies and acute exacerbations. These key drug therapy findings for chronic therapies and acute exacerbations were based on a level of evidence from the literature as determined by a consensus committee (References 15, 16).

Chronic Maintenance Therapy

Although CF is a disease of exocrine dysfunctional and CFTR abnormalities, the pulmonary manifestations of this disease are the most difficult to treat and account for most of the morbidity and mortality in patients with CF (Reference 17). Because this disease is progressive, therapies to maintain or preserve lung function and quality of life are now the mainstay of treatment. These approaches include the use of long-term inhaled antibiotics and bronchodilators, as well as chest physiotherapy and other methods to facilitate mucociliary clearance (Reference 15).

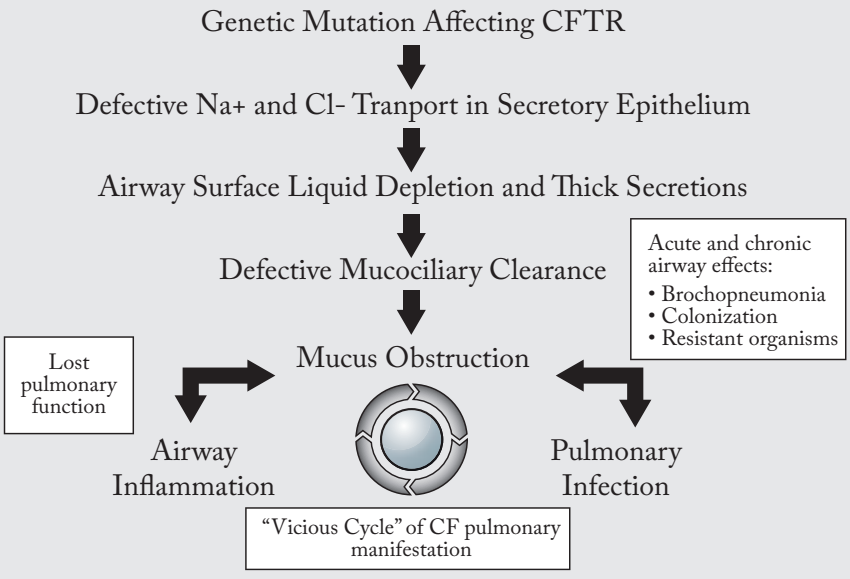


Figure 3. Pulmonary manifestation in CF.
CF = cystic fibrosis; CFTR = CF-transmembrane conductance regulator; Cl^- = chloride; Na^+ = sodium.

CHRONIC AEROSOLIZED ANTIBIOTICS

Inhaled antibiotics show long-term benefit in patients with PA colonization (Reference 12). For almost 50 years, patients with CF have received inhaled antibiotics. Initially, they were heroic approaches to very ill patients that involved parenteral formulations placed in traditional jet nebulizers by local centers (References 18–20). In 1999, the first inhaled aerosolized antibiotic, tobramycin solution for inhalation, was approved with a 300-mg dose twice daily, alternating every 28 days. Because the drug is directly administered to the airway and little systemic absorption occurs, larger doses of aminoglycosides can be used for chronic administration with little risk of long-term nephrotoxicity. Efficacy of this regimen has been shown in children 6–12 years of age as well as in those 13–18 years of age, with an average improvement in the FEV_1 of 11 (Reference 21). Potential adverse effects of tobramycin solution for inhalation include bronchospasm, hoarseness, and tinnitus. This was the only approved drug formulation until 2011, when aztreonam lysine was approved with a dose of 75 mg three times/day with a similar 28-day alternating-therapy regimen (References 22, 23). This alternating-day regimen was selected to minimize the development of resistance of PA and other sensitive isolates to these chronic therapies. Potential adverse effects of aztreonam lysine include bronchospasm, sore throat, nasal congestion, and fever (in children). Data from inhaled tobramycin document a rise in the minimum inhibitory concentration (MIC) of the PA isolated, but this increase, seen in the first few cycles, seems to plateau with time (Reference 24). Given that the aerosolized concentration in sputum is 50–100 times higher than microbiologic breakpoints and that it has a concentration-dependent killing of this organism, the clinical utility of these breakpoints may not be relevant to patient care (Reference 24). Currently, doses for tobramycin solution for inhalation and aztreonam lysine are standard for all age patients requiring therapy.

In addition, before the availability of approved aerosolized antibiotics, other parenteral formulations were used by aerosolized administration to medically manage patients with CF. Colistimethate has been used for almost 40 years in Europe as well as the United States as an aerosol with a dose of 75–150 mg two times/day (References 20, 25). Various formulations of this product have been used by centers around the world, and

with changing formulations of this natural product, adverse events have occurred, including bronchospasm. Therefore, many centers pretreat with albuterol before a dose of colistin, and careful respiratory monitoring is warranted with the first dose of this medication. Reconstitution of colistin should be done just before administration to minimize the potential formation of broncho-irritative metabolites.

As aerosolized antibiotics have developed during the past decade, nebulizer technology has dramatically changed, and improvements have been made to maximize the amount of drug delivered to the patient. Drug delivery can be greatly affected by different devices, and care should be taken to make sure the correct nebulizers are used to deliver the drug. Compressed gas-jet nebulizers were used with most nebulized antibiotics until recently. Piezoelectric cell vibrating-mesh nebulizers (e.g., Trio and Altera) now can deliver a uniform particle size aerosol in a very short time (Reference 26). Care must be taken not to universally interchange these devices for antibiotic aerosols or mix them with bronchodilators because performance can be greatly affected. The use of these new improved delivery systems will benefit patients with CF in the coming years, and this technology will help with the delivery of other inhaled medications.

other aerosolized agents

There are two agents that help increase the removal of the thick sputum produced by patients with CF by breaking down extracellular DNA or increasing the amount of fluid in the airway. Dornase alfa inhalation has also shown long-term benefit in preserving lung function as part of chronic therapy in CF. This compound works by hydrolyzing extracellular DNA in the sputum to decrease the viscosity of the sputum and improve sputum expectoration by the patient. It has been used for more than a decade with few adverse effects to patients and is one of the first aerosolized therapies initiated in young children with CF. This drug cannot be mixed with other aerosol medications because it often denatures the product, especially with hypertonic solutions.

Since the latest guidelines, studies with aerosolized 7% hypertonic saline have also shown benefit for chronic therapy, but long-term data (beyond 48 weeks) are currently lacking (Reference 27). Hypertonic saline works by increasing the volume of fluid on the epithelial lining of the airway to maintain normal ciliary flow and increase sputum expectoration. Hypertonic saline concentrations from 3% to 10% were studied, and a 7% solution was found to have the best response with a low rate of bronchospasm, the major adverse effect of this therapy. Some patients may only be able to tolerate 5% solutions, and concentration adjustments may need to be made on an individual basis. To our knowledge, no studies have addressed the concomitant use of these agents for chronic therapy.

anti-inflammatory therapy

The vicious cycle of infection and inflammation is now recognized as a key component of the pulmonary manifestations of CF. The focus has been on long-term anti-inflammatory therapy for patients with CF, although earlier studies with systemic corticosteroids showed improvement in lung function but with an unacceptable toxicity profile, with increases in hyperglycemia, osteoporosis, and growth retardation. Some clinicians use a short course of corticosteroids during an acute pulmonary exacerbation or other illness, but long-term use is not warranted. The use of high-dose, chronic ibuprofen in pediatric patients during a 4-year period showed a decrease in the rate of decline in pulmonary function (Reference 28). This approach, used in only a few patients today, requires pharmacokinetic dose monitoring of serum concentrations to maximize the dose. Serum concentrations of 50–100 mcg/mL are required to maximize the effect of this intervention (Reference 29). Because of concerns about the long-term toxicity of ibuprofen (e.g., gastrointestinal irritation and renal dysfunction), this therapy is not widely used.

In the past decade, the anti-inflammatory properties of azithromycin and other related compounds have been studied, and recent clinical studies have shown benefit in preservation of lung function and decreased pulmonary exacerbations (Reference 30). This therapy accentuates the anti-inflammatory properties of this drug, not its antimicrobial effect. Many patients, including young children, receive this therapy chronically either on a daily or every-other-day basis. According to the Cystic Fibrosis Foundation guidelines regarding chronic medications, patients with *P. aeruginosa* consistently in respiratory or sputum cultures should be considered candidates for chronic azithromycin therapy (Reference 15). Doses of 250–500 mg given three to seven times/week (not to exceed 10 mg/kg/day) are used by most CF clinicians for long-term therapy. Because the emphasis of this medication is on its anti-inflammatory effects, dosing can be adjusted for convenience because its effect is much longer than its serum half-life. Long-term therapy with azithromycin has not shown any direct adverse reactions. Recent data suggest that the chronic long-term use of azithromycin increases the incidence of nontuberculous mycobacterial infections in patients with CF. Azithromycin blocks autophagosome clearance, which facilitates the intercellular killing of mycobacteria (Reference 31). Careful follow-up of the CF population receiving azithromycin will help clarify the clinical impact of this observation.

Treatment of Acute Pulmonary Exacerbations

Despite the use of daily medications and airway clearance therapies, patients with CF often experience rapid clinical deterioration and increased respiratory symptoms. The increasing cycle of airway inflammation and mucus accumulation in the airway continues, and patients often experience increasing work of breathing, fever, increased mucus production, fatigue, and weight loss (Reference 12). This relatively rapid onset of symptoms is referred to as an acute pulmonary exacerbation. The hallmark of this disease has been that almost every patient experiences some episodes with variable frequency (e.g., four or five times/year and others, with milder disease, having an exacerbation every 2–3 years). Complete eradication of bacterial and other microbes in the airways becomes more challenging with increased age and/or incidence of pulmonary exacerbations; thus, the selection of antimicrobial treatment is a common challenge in the treatment of CF pulmonary exacerbations.

ANTIBIOTIC SELECTION

At present, acute pulmonary exacerbation is not well defined, and no clear consensus has been reached regarding what antibiotics should be prescribed or whether the therapy should be inpatient or outpatient. The choice of antibiotics is directed at the most common organisms found in the respiratory tract of each patient because most patients undergo routine quarterly sputum culture collections. Two important caveats in the surveillance and selection of antibiotics should be noted. First, traditional sensitivity results do not predict clinical success of patients with resistant organisms. This was described 20 years ago in a study comparing treatment with antibiotics versus placebo for acute pulmonary exacerbations, which found no difference in short-term pulmonary function changes (Reference 32). Other studies have confirmed improvement with antibiotics—usually dual antipseudomonal therapy and additional antibiotics directed at other microbiologic isolates (References 33, 34). Second, less robust evidence is available to validate the benefit of the duration, number of antibiotics, dosing strategy, and environment of treatment (e.g., inpatient vs. home therapy for the treatment of acute exacerbation) (Reference 16). Given this background, most centers still use two-drug antipseudomonal therapies for exacerbation in PA-positive patients for at least 10–14 days. The overall improvement in life expectancy and preservation of lung function globally in the CF community for the past 20 years has been an important observation to continue this practice of dual antipseudomonal therapy. Current guidelines from a consensus conference by the Cystic Fibrosis Foundation support the use of antibiotics, but they do not endorse two drug treatments over one susceptible drug. Treatment guidelines have focused on patients with PA, and many patients harbor several other gram-negative organisms and very difficult-to-treat organisms such as *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, and methicillin-resistant *S. aureus* (MRSA), making antibiotic selection complex. Antibiotic selection can be guided, but not dictated, by the results of microbiologic testing. Current practice at most centers would use dual antipseudomonal drug therapy for synergy. During the past 2 decades, several reports of rapid clearance of aminoglycosides and semisynthetic penicillins have been described in patients with CF; therefore, recommended doses of these agents are higher than in patients without CF. Consensus guidelines suggest that once-daily high-dose aminoglycosides like tobramycin at a starting dose of 10 mg/kg/day are warranted (Reference 16). As a patient's weight changes with growth, the previous pharmacokinetic parameters can be used to adjust doses and determine clearance with subsequent serum concentrations. Once-daily aminoglycoside therapy in CF results in a lower occurrence of nephrotoxicity, as defined by increased serum creatinine and urinary NAG (*N*-acetyl-β-D-glucosaminidase), compared with thrice-daily dosing (Reference 35). No changes in pulmonary function were seen between the two groups. Of importance, given the short half-life of tobramycin and other aminoglycosides, single daily doses will result in a very long time below the MIC in many pediatric patients. Although the postantibiotic effect of tobramycin against mucoid PA is not clearly understood, it certainly does not exceed 4–6 hours. Therefore, in some patients with very rapid clearances (e.g., with a half-life of less than 2 hours), some centers administer doses of 6–8 mg/kg every 12 hours to shorten this postantibiotic period and still allow substantial clearance of the drug (Reference 36). In any case, careful monitoring of serum concentrations is necessary to prevent accumulation and potential nephrotoxicity and ototoxicity. Recent work suggests that patients with CF are indeed candidates for vestibular loss, especially given the many courses of aminoglycosides they have received (Reference 37). With the tremendous increase in life expectancy, the next decade will tell whether total dose or dosing regimens played the most important role in toxicity. Table 2 includes various doses of drugs used for chronic administration and for managing these acute exacerbations in patients.

Because most of the morbidity and mortality with CF is related to lung decline and deterioration, strategies are now being applied to CF from other diseases and conditions. Continuous-infusion antibiotics with concentration-dependent killing or prolonged infusion of these antibiotics are now being used with intermittent high-dose aminoglycosides to help maximize the treatment of PA exacerbations and other organisms

Table 2. Antibiotics and Dosing Regimens Commonly Used in the Treatment of Acute Pulmonary Bacterial Exacerbations in Patients with Cystic Fibrosis[a]

Antibiotic	Dosing Regimen[b]
For *Pseudomonas aeruginosa*	
Amikacin	7.5–10 mg/kg/dose IV q8h[c] or 30 mg/kg/day
Aztreonam	50–70 mg/kg/dose IV q8h (up to 8 g/day)
Cefepime	50–70 mg/kg/dose IV q8h (up to 2.5 g/dose)
Ceftazidime	50–70 mg/kg/dose IV q8h (up to 8 g/day)[d]
Ciprofloxacin (IV)	10 mg/kg/dose IV q8h (up to 400 mg/dose)
Ciprofloxacin (oral)	40–50 mg/kg/day PO q8–12h (up to 750 mg/dose)
Colistin	3–6 mg/kg/day IV q8–12h
Imipenem/cilastin	25–40 mg/kg/dose IV q6h (up to 1 g/dose)
Levofloxacin	Children 7–10 mg/kg/day IV or PO q24h Adults 500–750 mg/day IV or PO q24h
Meropenem	40 mg/kg/dose IV q8h (up to 2 g/dose)
Piperacillin/tazobactam	300–500 mg/kg/day IV q4–6h (up to 24 g/day)[e]
Ticarcillin/clavulanate	300–500 mg/kg/day IV q6–8h (up to 24 g/day)[e]
Tobramycin	10 mg/kg/dose IV q24h[c] or 6–7 mg/kg q12h
For *Staphylococcus aureus*, methicillin resistant	
Daptomycin	Should not be used for acute exacerbations
Linezolid	Children 10 mg/kg/dose IV or PO q8h Adults 600 mg IV or PO q12h
Tigecycline	Children – N/A Adults – 100 mg loading dose; then 50 mg IV q12h
Vancomycin	15–20 mg/kg/dose IV q6–8h
Inhaled Drugs	
Aztreonam lysine for inhalation	75 mg inhaled three times/day for 28 days; then off for 28 days
Dornase alfa	2.5 mg inhaled daily
Hypertonic saline 7%	4 mL inhaled twice daily
Tobramycin solution for inhalation	300 mg inhaled twice daily for 28 days; then off for 28 days

[a]Combination therapy is recommended.
[b]Doses assume normal renal and hepatic function. Dose adjustment may be necessary for renal and hepatic impairment.
[c]Use of historical therapeutic milligram-per-kilogram dosage if available.
[d]Reference 38.
[e]Based on piperacillin or ticarcillin component.
h = hours; IV = intravenous(ly); N/A = not applicable; PO = orally; q = every.

(Reference 39). Practical solutions for ambulatory patients are now available, and many patients can finish their course of antibiotics at home or may receive the entire course at home after a clinic visit. This is particularly true of adults with CF given their work and school demands. No definitive study has been conducted with these approaches to date, but given the success of these strategies in other pulmonary infections, such studies may be of considerable long-term benefit to patients with CF.

Therapy duration is usually determined by careful monitoring of overall symptoms and improvement in pulmonary function (e.g., FEV_1), with treatment often lasting 10–14 days (References 16, 40). Patients often have a serial pulmonary function test every few days to show improvement as well as symptom improvements and weight gain. Many clinicians are following biomarkers like C-reactive protein and procalcitonin to evaluate the progress of an exacerbation, especially for patients in whom pulmonary function testing may be difficult. In one recent study, lower procalcitonin was correlated with patient improvement (Reference 41). Therapy can continue beyond this time if the patient's clinical course does not improve significantly and/or changes in antimicrobial agents are required.

Monitoring of pulmonary therapy

A return to baseline FEV_1 after recovering from a pulmonary exacerbation is ideal but not always possible—thus, the importance of continued suppression of inflammation and infection through airway clearance and accompanying drug therapy (Reference 42).

Because of the aggressive and often-repeated nature of antimicrobial courses, patients with CF require careful monitoring both for long- and short-term events. Initial serum concentrations should be obtained within the first 72 hours of therapy unless the patient has a history of delayed clearance or nephrotoxicity. At some CF care centers, it is common to wait 2–3 days to make sure the patient has been adequately rehydrated because many of the patients have had decreased oral intake and increased losses with their increasing symptoms during the previous 5–7 days. Because of the increased incidence of MRSA and PA sputum isolates with pulmonary exacerbation, patients are often treated with intravenous vancomycin in combination with an aminoglycoside. These patients should be monitored often, with care taken for drug accumulation and increased trough concentration during the traditional 10–14 days of therapy. With increasing age and a larger incidence of CF-related diabetes (CFRD), a decrease in aminoglycoside clearance should be anticipated with time. Whether this is caused by age or cumulative toxicity is unclear, but as care moves to adult centers and physicians, previous dosing of drugs should be adjusted accordingly.

Nutrition in CF

Physical Manifestations

Because of defective CFTR and subsequently impaired transport of Na^+ and Cl^- resulting in viscous epithelial secretions, the pancreatic duct becomes obstructed. This obstruction prevents proper secretion of pancreatic enzymes into the digestive tract, otherwise known as pancreatic insufficiency. Chronic pancreatic insufficiency is a common complication affecting around 85% of individuals with CF (Reference 43). Pancreatic insufficiency causes malabsorption of fat and protein, leaving individuals with CF to face challenges in nutritional status. This decrease in nutrient absorption subsequently leads to overall poor growth and, potentially, failure to thrive, especially in infants and younger children. In addition to fat malabsorption, fat-soluble vitamin (i.e., vitamins A, D, E, and K) deficiency is common. Pancreatic damage, including pancreatitis, can also manifest because of defective pancreatic exocrine secretion (References 44, 45). Other complications secondary to nutrient malabsorption caused by CF include anemia (often iron-deficient) and osteopenia or osteoporosis.

Caloric Needs and Nutritional Status in CF

Individuals with CF often face challenges of poor nutritional status, including poor growth (i.e., weight, stature, and weight-for-stature) and vitamin deficiency. Infants and young children with CF are at increased risk of failure to thrive. Older children and adolescents also face challenges of poor growth because of nutritional risk secondary to CF. Energy needs in this population are increased because of expenditure secondary to their pulmonary condition, including chronic cough, infection, and increased work of breathing. Thus, it is highly recommended that children with CF be provided greater dietary energy intake than children without CF. Weight gain and growth have been shown with intakes from 110% to 200% that of healthy individuals. High-calorie or calorically dense foods, such as fortified infant formulas or breast milk for infants and full-fat dairy products and proteins for children and adults, are encouraged. Consistent, high-calorie dietary intake can be a challenge in patients with CF because of several physiologic factors, including loss of taste or smell caused by chronic sinusitis and chronic gastroesophageal reflux. In addition, behavioral factors may affect intake, which can require behavioral intervention by nutritionists and/or psychologists. For patients of all ages with continued suboptimal growth, use of enteral feeding modes may also be necessary, commonly provided by a gastrostomy tube (i.e., G-tube). With enteral feeding, concentrated, calorically dense formulas may be used to provide more calories with less volume.

Therapies for Nutrition Challenges in CF

Pancreatic Enzyme Replacement Therapy

A diagnosis of pancreatic insufficiency includes genotype evaluation (i.e., two mutations associated with pancreatic insufficiency), growth failure, symptoms including steatorrhea (fatty stool), and measurement of fecal elastase. Measurement of fecal elastase is used for diagnosis versus monitoring of enzyme replacement efficacy. Because fecal elastase involves a general measurement, it is not used for assessing therapy efficacy because it is not a quantitative test. Fecal elastase values less than 200 mcg/g are indicative of pancreatic insufficiency (Reference 46). The 72-hour fecal fat test is an option for quantifying fat malabsorption. However, this approach is not commonly used because it is tedious for caregivers and potentially poor in accuracy (Reference 43).

The mainstay of therapy for pancreatic insufficiency caused by CF is pancreatic enzyme replacement therapy (PERT). These supplements should be taken or administered at meal and snack times, as well as in coordination with enteral feeds if this mode of nutritional provision is used. Pancreatic enzyme formulations contain different combinations of lipase, protease, and amylase from porcine sources (Table 3). Although once thought of as dietary supplements and previously poorly regulated in manufacturing and labeling, CF PERT products are now reviewed for approval by the U.S. Food and Drug Administration (FDA). The movement toward full review of PERT products arose because of inconsistencies regarding enzyme concentrations between brand and generic formulations. The Cystic Fibrosis Foundation does not recommend the use of generic PERT preparations because of therapeutic failure, secondary to unregulated manufacturing (References 43, 55). The beads or microspheres within the dosage forms (i.e., capsules) are often enteric coated to protect them from acid-mediated destruction in the stomach. This coating dissolves in the less acidic environment of the duodenum, where the enzymes act to aid in digestion and nutrient absorption (i.e., fats, protein, carbohydrates) (Reference 56). Dosing of PERT is weight-based and dependent on the lipase component of dosage forms. The recommended starting dose for children younger than 4 years is 1000

Table 3. Examples of Pancreatic Enzyme Replacement Dosage Forms Used in Cystic Fibrosis (References 47–54)

Brand Name	Amounts in Units per Dosage Form		
(dosage form)	Lipase	Protease	Amylase
Creon	3000	9500	15,000
(capsules with enteric-coated, delayed-release microspheres, porcine derived)	6000	19,000	30,000
	12,000	38,000	60,000
	24,000	76,000	120,000
Pancreaze	4200	10,000	17,500
(capsules with enteric-coated, delayed-release microspheres, porcine derived)	10,500	25,000	43,750
	16,800	40,000	70,000
	21,000	37,000	61,000
Pertzye	8000	28,750	30,250
(capsules with enteric-coated, bicarbonate buffered, delayed-release capsules; porcine derived)	16,000	57,500	60,500
Ultresa	13,800	27,600	27,600
(capsules with enteric-coated, delayed-release microspheres; porcine derived)	20,700	41,400	41,400
	23,000	46,000	46,000
Zenpep	3000	10,000	16,000
(capsules with enteric-coated, delayed-release microspheres; porcine derived)	5000	17,000	27,000
	10,000	34,000	55,000
	15,000	51,000	82,000
	20,000	68,000	109,000
	25,000	85,000	136,000

units of lipase per kilogram per meal. For children 4 years and older, a starting dose of 500 units of lipase per kilogram per meal is recommended. Doses should not usually exceed 2500 units of lipase per kilogram per meal, with a maximum of 10,000 units of lipase per kilogram per day (References 55, 57). When doses are approaching or exceeding usual maximum doses, further assessment of adherence, administration technique, or other potential gastrointestinal comorbidities is recommended. Doses are primarily adjusted on the basis of patient response, with efficacy assessment including patient weight and/or growth markers (e.g., body mass index [BMI]), frequency of stools, stool consistency (e.g., loose vs. formed), abdominal symptoms (e.g., cramping), and incidence of steatorrhea. Dosing for snacks depends on the size and components (i.e., fat content) of the snack. For example, if a snack is about one-half the size of a meal, 50% of the meal dose should be given. However, some patients with CF consume equal-sized portions throughout the day, including both meals and snacks. In these cases, the snack dose would be equivalent to meal dosing.

If PERT dosing requirements exceed recommended meal or daily maximums, further investigation about other factors affecting efficacy may be necessary. These factors include adherence, diet, and other comorbidities that may affect GI symptoms such as loose stools, steatorrhea, or abdominal cramping (Reference 57). When other possible causes of treatment failure are ruled out, the efficacy of PERT should be considered. The efficacy of PERT can vary on the basis of GI tract pH; thus, comorbidities such as gastroesophageal reflux may influence therapy outcomes. When maximal dosing is reached, other etiologies are excluded, and the individual continues to present with symptoms of malabsorption (e.g., steatorrhea), the use of long-duration acid suppression by a proton pump inhibitor may aid in "boosting" the effect of PERT. Studies showing improved growth and decreased incidence of steatorrhea with the addition of a proton pump inhibitor are part of the literature of children as young as 3 years. Dosing is similar to usual starting doses for treatment of gastroesophageal reflux disease (GERD) (e.g., for a 4-year-old with a weight of 13 kg starting omeprazole 10 mg orally daily) with an indefinite duration because the medication is used to aid in the effect of lifelong PERT (References 56, 58, 59). Taurine is an oral supplement that has been proposed as a possible adjunctive therapy when response to PERT is poor, resulting in fat malabsorption. The proposed mechanism of its effect originates in its properties as an organic acid and a component of bile. Data are conflicting regarding its efficacy for enhancing fat absorption in CF; thus, its use is not routinely recommended until further data show benefit (References 60, 61).

Vitamin Supplementation

As part of the malabsorption of nutrients secondary to pancreatic insufficiency, specifically fat, a deficiency in fat-soluble vitamins is a common nutritional complication. Oral supplementation of vitamins A, D, E, and K in individuals with CF, especially those with pancreatic insufficiency, is recommended (Reference 43). This supplementation is often provided by a specific multivitamin containing greater amounts of vitamin A, D, E, and K (e.g., AquADEK, Vitamax, and Source CF), with dosing based on age and product formulation. Individuals deficient in these vitamins may be asymptomatic; thus, the use of laboratory tests to assess status is recommended (Reference 43). Vitamin A is important for several different functions including vision, immune function, and growth. Measurement of the serum level of retinol, a marker of vitamin A, is recommended at least annually. For many patients with CF, supplementation by a CF-specific multivitamin containing water-miscible vitamins A, D, E, and K is sufficient for needed supplementation. Excess vitamin A has been associated with bone and liver disease (Reference 62). Additional oral vitamin A can be provided in doses from 1500 up to 10,000 units/day, depending on age and deficiency (Reference 43).

Vitamin D is necessary for bone health and other functions such as immune function. Deficiency of vitamin D often requires additional oral supplementation with vitamin D_3 (cholecalciferol) or vitamin D_2 (ergocalciferol), ranging from 400 IU to 1000 IU/day to weekly high-dose regimens (e.g., 50,000 IU). Although many forms of vitamin D are available for use by prescription or over the counter, it has been noted that vitamin D_3 is better absorbed and thus perhaps more efficacious than vitamin D_2 for supplementation in deficiency (References 63, 64). Measurement of serum concentrations of vitamin D (i.e., 25-OH-D) are recommended at least annually as part of standard care for patients with CF, with goal concentrations of 35–60 ng/mL (87.5–150 nmol/L) and provision of additional supplementation for concentrations below 35 ng/mL (87.5 nmol/L) (References 43, 65).

Vitamin E, with its function as an antioxidant, also has a postulated role in suppressing inflammation. Similarly, measurement of a serum level (i.e., α-tocopherol) is recommended at least annually. Because patients with CF often have lower cholesterol levels than individuals without CF, more accurate assessment of vitamin levels may be achieved by use of an α-tocopherol/cholesterol ratio. Additional vitamin E oral supplementation, when levels are low despite standard CF supplementation, can be provided in doses of up to 400 units/day, depending on age and deficiency (Reference 43).

Vitamin K, necessary as a cofactor for the coagulation pathway, is often deficient in individuals with CF because of fat malabsorption as well as changes in GI flora. In individuals with CF-associated hepatobiliary disease, this deficiency may be further exacerbated, requiring additional oral supplementation (e.g., phytonadione). Additional oral supplementation of vitamin K may be needed for older children and adults with CF who have chronic deficiency based on laboratory values, who are given long-term antimicrobial therapy, or who have an ongoing history of hemoptysis (Reference 66). Additional vitamin K or phytonadione oral supplementation can be provided in doses ranging from 2.5 to 10 mg/day, depending on age (Reference 43). Monitoring of serum levels of prothrombin or PIVKA-II (proteins induced by vitamin K absence) is suggested at least annually, with PIVKA-II being more sensitive; however, PIVKA-II may not be easily accessible at all institutions (Reference 43).

Appetite Stimulants

For some individuals, dietary intake to reach or maintain nutritional goals in CF is a chronic challenge because of inadequate appetite. Etiology of poor appetite is variable and can be psychological (e.g., depression), result from an adverse effect of a medication (e.g., methylphenidate, bupropion), or be caused by another comorbidity such as poor GI motility (e.g., gastroparesis). Individuals with CF at nutritional risk (i.e., BMI percentile, 25% or less) should be evaluated appropriately before appetite stimulants are initiated. Dietary intake review (e.g., food diaries), laboratory workup for other comorbidities (e.g., CFRD, GERD), and evaluation of psychosocial or socioeconomic status should be part of the assessment for appropriateness of appetite stimulants (Reference 67).

Treatment of the source of poor appetite or oral intake is ideal (e.g., treatment of depression); however, in certain instances, the employment of appetite stimulants may be considered if the use of primary approaches fails to result in improvement. Agents used as appetite stimulants in CF include those used in patients with cancer (e.g., megestrol acetate, cyproheptadine). These agents each possess useful effects of appetite stimulation and weight gain that are useful for individuals with CF who are challenged in weight gain and poor oral food intake. Choice of agent will depend on patient-specific factors such as age, available data, and dosage form needed (e.g., liquid vs. tablet). Safety and efficacy of agents such as cyproheptadine have been studied for as long as 12 months in some children (Reference 68). Dronabinol, the oral dosage form of delta-9-tetrahydrocannabinol, is another potential agent used in patients with cancer and patients with AIDS (acquired immunodeficiency syndrome) wasting syndrome. However, documented use of this agent in the CF population as an appetite stimulant is limited, with greater experience in adolescents and adults with CF and use of doses of up to 5 mg by mouth twice daily (Reference 69). Other agents that could be considered for use include the antidepressant mirtazapine at doses of up to 45 mg/day orally, with most experience in adolescents and adults with CF (References 70, 71). Antipsychotics such as olanzapine and risperidone have also been used in patients with CF because they have a strong adverse effect of excessive weight gain (Reference 72).

Monitoring Nutritional Therapy

Nutritional status is of upmost importance for children with CF because of the association between normal weight and stature for age and improved FEV_1 and survival. The Cystic Fibrosis Foundation recommends that children with CF be in at least the 50th percentile in weight-for-length during the first 2 years of life and that individuals with CF who are 2–20 years of age maintain at least the 50th percentile or higher for BMI to optimize FEV_1 (References 43, 55). Some CF centers have developed color-coded growth charts (Figure 4) to help facilitate the monitoring of nutritional risks on the basis of guidelines and cite specific designated progression of nutritional risk (References 43, 55, 73). Additional laboratory monitoring is recommended to assess the nutritional status of individuals with CF. Tests that should be performed upon diagnosis and at least annually include vitamin levels, albumin and prealbumin for assessment of protein stores, and hemoglobin and hematocrit for basic assessment of potential iron-deficiency anemia. Additional workups of iron-deficiency (e.g., total iron-binding capacity, total ferritin level) anemia may be considered. Other laboratory tests to consider include serum sodium in cases of potential dehydration and essential fatty acids in cases of poor nutritional status. Because patients with CF are at increased risk of osteopenia, the use of tests to assess bone mineral density (e.g., DXA [dual {energy} x-ray absorptiometry]) may be warranted (Reference 43).

Other GI Diseases in CF

Physical Manifestation

With the obstruction of the pancreatic duct caused by viscous epithelial secretions, some neonates with CF may exhibit an early GI manifestation of CF known as meconium ileus. Meconium ileus is an obstruction of the small intestines by meconium, the early stool of a neonate composed of ingested material including mucus, amniotic fluid, and bile. With a less common occurrence, meconium ileus presents in only 10% to 15% of patients with CF. Distal intestinal obstruction syndrome (DIOS)

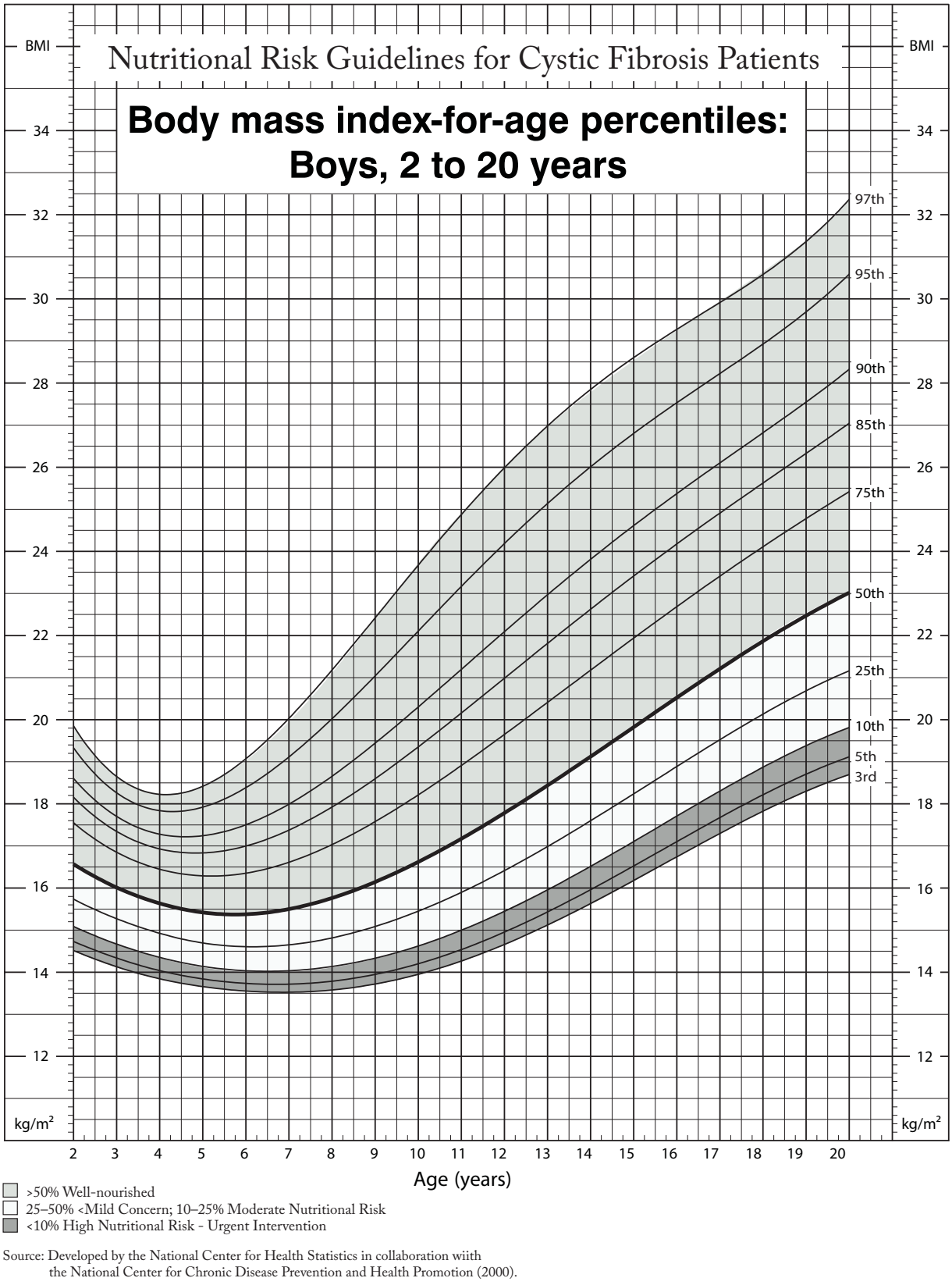


Figure 4. Centers for Disease Control and Prevention body mass index-for-age, boys 2–20 years, adapted for patients with cystic fibrosis nutritional risk (References 73, 74).

is the meconium ileus equivalent in children and adults with CF. Individuals with a history of meconium ileus may be at increased risk of developing DIOS. In DIOS, intestinal contents (e.g., fecal matter) block the small intestinal lumen, and its etiology is not completely understood. Proposed etiologies of DIOS include pancreatic insufficiency and decreased intestinal motility. Other complications that may or may not accompany DIOS include intussusceptions and rectal prolapse (References 75, 76). Rectal prolapse, associated with malnutrition, constipation, and diarrhea, is another GI complication reported in about 20% of individuals with CF. This most commonly occurs in younger children (e.g., 1–3 years of age), and it is often transient, frequently resolving at 3–5 years of age (Reference 77).

Small intestinal bacterial overgrowth (SIBO) is a condition in which bacterial content increases, resulting in damage to enterocytes and worsening malabsorption and malnutrition, with an incidence as high as 30% to 50% in the CF population (Reference 78). Although SIBO is also seen in patients without CF, individuals with CF are at risk of SIBO because of the potential for poor intestinal motility and use of thrice-weekly azithromycin as part of a chronic pulmonary management regimen (References 75, 76).

Obstruction of the biliary duct and accumulation of viscous bile can lead to focal biliary cirrhosis in 11% to 70% of individuals with CF; however, it is not always apparent because some individuals may be asymptomatic (Reference 79). Like other areas throughout the body where epithelium is located, CFTR is also found in biliary epithelial cells. As a result, bile ducts are obstructed because of viscous bile production, which causes cholelithiasis, cholecystitis, progressive fibrosis, and cirrhosis. In neonates with CF, cholestasis may result, which is sometimes mistaken for biliary atresia. Individuals with CF-associated hepatobiliary disease may also develop steatosis (i.e., fatty liver) because of various factors including essential fatty acid deficiency or malnutrition. Further complications, including portal hypertension, can be found when CF-associated hepatobiliary disease is symptomatic and severe (References 79, 80). With the increased life expectancy of CF, the incidence of CF-associated hepatobiliary disease may increase because this complication is often found in older children and adults with CF. Evaluation of liver enzymes, including γ-glutamyl transferase at least annually in stable patients with CF, is recommended. For individuals who present with persistent elevations, further investigation is warranted, including an assessment of clinical presentation (e.g., stool pattern, jaundice, abdominal pain) and other possible etiologies such as other GI disorders or medication-induced liver injury. Additional testing including imaging evaluation, upper GI endoscopy, or biopsy may be employed to confirm diagnosis.

Gastroesophageal reflux disease is also a common comorbidity among individuals with CF, with an incidence as high as 58% to 86% (Reference 81). It is postulated to be attributable to various causes, including transient relaxation of the lower esophageal sphincter and increased intra-abdominal pressure because of chronic cough. Not only does GERD potentiate the risk of poor nutrition in young children with CF, but it may also pose a risk of other complications such as gastric aspiration (References 81, 82). The diagnosis of GERD in children with CF is similar to the diagnosis of GERD in children without CF.

Therapies for GI Diseases in CF

DIOS and Rectal Prolapse

Proposed causes of DIOS include iatrogenic decrease of intestinal motility, or abnormalities in fluid and electrolyte balance of secretions in the GI tract, resulting in viscous, mucous-like obstruction. Constipation is often associated with DIOS, and definitions separating the two conditions have been outlined in formal guidelines (Reference 83). Unlike constipation, in which the use of laxatives (e.g., oral polyethylene glycol, lactulose) often alleviates the condition, DIOS often necessitates the use of more aggressive treatment, including laxatives at higher doses, use of electrolyte intestinal lavage solution (e.g., GoLYTELY), or hyperosmolar enemas. Oral *N*-acetylcysteine (5% solution) has also been used for the prevention and treatment of mucus accumulation in the GI tract of some individuals with DIOS (References 83, 84). Distal intestinal obstruction syndrome is thought to be related to pancreatic insufficiency that is poorly controlled with PERT. Similarly, rectal prolapse may respond to an increase in PERT dose and seldom requires surgical intervention (Reference 77).

Small Intestinal Bacterial Overgrowth

Treatment of SIBO in individuals with CF is also similar to that of individuals without CF, such as the use of oral antibiotics (e.g., rifaximin, metronidazole, norfloxacin). Treatment may help improve the nutritional status of patients with CF. Additional treatment modalities may include dietary manipulation, such as reducing carbohydrate consumption, resulting in a high-fat, low-carbohydrate diet. The use of laxatives and inhaled ipratropium has also been associated with a decreased risk of SIBO (Reference 85).

Hepatobiliary Disease

As part of the treatment of hepatobiliary disease in CF, it is imperative to optimize nutrition, especially fat-soluble vitamin and essential fatty acid deficiencies (Reference 72). In addition to nutritional support, treatment with oral ursodeoxycholic acid or ursodiol (20 mg/kg/day

divided three times/day) is currently recommended; however, additional outcomes data are necessary to describe its long-term effect on cholestasis, fibrosis, and cirrhosis in CF (Reference 86). Taurine, an organic acid found in bile, has also been proposed for adjunctive treatment of hepatobiliary disease in CF; however, limited data support its routine use for this purpose (Reference 61).

Gastroesophageal Reflux Disease

If symptoms of GERD coincide with poor nutritional status (e.g., failure to thrive), treatment is warranted, especially in infants and younger children. Medical management of GERD in children with CF is similar to that in other children without CF, including initial use of histamine-2 receptor blockers (e.g., ranitidine) (Reference 87). However, for some patients with CF, management can be more severe, requiring a change to or addition of a proton pump inhibitor (e.g., lansoprazole). Surgical management of GERD by fundoplication is also considered when complications are severe such as erosive esophagitis, uncontrolled pulmonary condition caused by reflux, or failure to thrive despite medical management (Reference 88).

Other Complications of CF

CF-Related Diabetes

The pathophysiology of the pancreatic disease also involves endocrine function or insulin regulation. Eighty-five percent of patients with CF have pancreatic enzyme insufficiency, and as the cystic changes in the pancreas progress, patients begin to have problems with insulin regulation. Patients with CF develop glucose intolerance as either fasting hyperglycemia or postprandial hyperglycemia. Routine screening is now recommended starting as young as 10 years of age, although some centers are starting even earlier in life because of potential variability in the clinical onset of this manifestation (Reference 89). A fasting blood glucose and a 2-hour postoral glucose load (e.g., glucose tolerance test) are recommended annually. Almost 30% of patients with CF older than 30 years have some form of glucose intolerance. As patients with CF continue to live longer, a higher percentage of them are expected to present with CFRD. This condition is not classic type 1 or 2 diabetes mellitus. Cystic fibrosis–related diabetes can often be initially managed with dietary restrictions from concentrated sugars (e.g., soft drinks). If this approach does not work, insulin is the drug of choice. Cystic fibrosis–related diabetes insulin therapy often involves modest doses of long-acting insulin paired with carbohydrate counting and coverage with rapid-acting insulin (Reference 90). Like with other patients with diabetes and an infection, an acute pulmonary exacerbation or illness may complicate glucose control, especially when systemic corticosteroids are used during the management of severe pulmonary exacerbations. Addressing issues related to blood glucose control is now paramount in the long-term management of CFRD (References 91, 92).

Chronic Sinusitis

As part of the upper respiratory tract, the sinuses are also affected in the inflammation and infection processes of CF. This is because of their pseudostratified ciliated epithelium and lack of mucociliary clearance as similarly seen in the airways. Individuals with CF often have hypoplasia of the sinuses, which creates a confined area where respiratory pathogens such as PA can remain, causing chronic infection and inflammation. Sinuses can be assessed by a computed tomography scan to confirm the diagnosis of sinonasal disease before treatment or surgical intervention because the sinuses can appear opacified by 8 months of age with conventional sinus radiography (Reference 93). Treatment of the acute exacerbations of sinusitis can include oral and/or intravenous antibiotics, which are also used in pulmonary exacerbations and in intranasal irrigations of antimicrobials such as gentamicin and amphotericin B.

Hyponatremia

The sudoriferous (sweat) glands, an epithelial exocrine system, are also affected by CF. Sweat from individuals with CF contains an abnormally high amount of Na^+ and Cl^- caused by the defective Cl^- impermeability of epithelial cells because of dysfunctional or absent CFTR. Thus, these individuals are at increased risk of electrolyte imbalances (e.g., hyponatremia, hypochloremia) during periods of heavy sweat excretion (e.g., warm weather combined with strenuous exercise) (Reference 94).

Because of the excessive loss of Na^+ in sweat, infants with CF are at risk of developing hyponatremic, hypochloremia dehydration. Infant formulas and breast milk do not provide adequate Na^+ for infants with CF; thus, it is recommended that ⅛ teaspoon of table salt be provided from birth and increased with time to ¼ teaspoon by 6 months through 1 year of age, divided throughout the day by feedings (Reference 46). Additional supplementation may be necessary for any patient living in high-temperature climates, especially patients involved in physical activities in these environments (e.g., athletes) (Reference 43).

Special Topics Related to CF

CF in Adulthood

As patients with CF grow older, complications arise, such as progressive respiratory disease and increased incidence of CFRD and insulin therapy. Additional chronic changes in the destructive nature of the lung in CF (e.g., bronchiectasis) develop, and patients often require

supplemental oxygen therapy and increased frequency of airway clearance. Osteoporosis is often seen in adult patients with CF because of inadequate intake or absorption or chronic hypoxia. Pharmacists in adult CF centers can be invaluable resources to help manage these complications, together with the CF care team.

Males with CF are infertile, but females can conceive and carry children to term. However, the fertility rate of females is reduced compared with that of patients without CF, partly because of the alteration of their cervical mucus, which impairs fertilization. Women with CF and severe lung disease have a higher risk of pregnancy complications (Reference 95). Therefore, it is important to address contraception in CF and explain the options for patients.

New Therapies

During the past 10 years, a tremendous partnership with the Cystic Fibrosis Foundation and the pharmaceutical industry has produced many new pharmaceuticals for clinical evaluation including aerosolized antibiotics, anti-inflammatory agents, and, most recently, agents that alter CFTR function. Some of these agents are new aerosolized formulations of antibiotics (e.g., tobramycin and amikacin), whereas novel compounds that help CFTR reach the airway surface in larger quantities are referred to as corrector drugs. Compounds that increase CFTR transport or function are referred to as potentiators of CFTR function (Reference 96). Early results of phase II trials of patients who are homozygous F508del mutation, with the combination of VX-809 (a corrector drug) in combination with VX-770 (a potentiator drug), have shown statistical changes in sweat chloride, a marker of Cl^- function (Reference 97). This approach to increasing CFTR activity at the airway surface and correcting abnormal CF has the potential to radically change how the disease can be managed, and it may profoundly affect survival and quality of life.

Recently, ivacaftor (formerly known as VX-770) was approved by the FDA for chronic therapy in patients with the G551D genotype of CF. Because this drug is a potentiator of this "gating" mutation of CF, therapy is limited to about the 4% of patients with CF having this genotype. It is given orally at a dose of 150 mg twice daily, taken with a fat-containing meal. Clinical trials showed an improvement in FEV_1 of 10% to 12% (Reference 98). Studies are ongoing with ivacaftor and other compounds to see whether other genotypes of CF will respond to this therapy.

In addition, the development of novel approaches continues in the delivery of gene therapy (e.g., corrected CFTR delivery) to the airway. Problems with vectors and host response to repeated doses continue to be an issue, but new approaches may be able to overcome these limitations of repeated dosing. The promise of these new therapies is indeed exciting and may provide the foundation for a profound change in the outlook of CF in the next decade (Reference 96).

Adherence in CF

Adherence to airway clearance and medication therapy is a lifelong challenge for many individuals with CF. Factors affecting adherence are often variable, making adherence difficult to effectively address in the care of patients with CF. Factors can be age-associated, with different reasons for nonadherence to therapies between an infant or small child compared with an adolescent. In the care of an infant or child, caregivers are primarily responsible for therapy administration. As a result, reasons for nonadherence in these instances include forgetting treatments, becoming confused because of several caregivers' responsibilities, discontinuing treatment in response to lack of symptoms, experiencing resistance from the child, developing concerns about medication adverse effects, and misunderstanding the instructions (Reference 99). Conversely, in older patients such as adolescents, self-administration is commonplace, and reasons for nonadherence are more personal and psychosocial. The balance of growing independence and continued parental involvement becomes a challenge for some families. In adolescents, risk-taking behavior, an invincible perspective, or peer influence may negatively affect treatment adherence. When considering the active lifestyles of youth, time can be a limiting factor affecting adherence, especially with respect to airway clearance therapy (Reference 100).

Patient-specific factors including socioeconomic status, culture, and/or caregiver beliefs can also affect adherence to both airway clearance and medication therapies. Studies have shown a potential preference for which therapy patients are adhering to. Medications that may provide perceived immediate relief, or results such as pancreatic enzymes, dornase alfa, albuterol, or hypertonic saline may be missed less often than those that provide conceived long-term benefit such as aerosolized antibiotics or even airway clearance (References 99, 101, 102). Many individuals with CF carry a heavy medication burden, which affects patient adherence to regimens. Polypharmacy is often encountered in the treatment of aggressive CF disease; however, despite the good intention of efficacy, combinations of medications can also place patients at increased risk of adverse drug events. Regular assessment of medication regimens is necessary as part of continued care.

Consequences of poor adherence to airway clearance and medication treatment can include increased frequency of exacerbations and increased rate of decline of lung function. Medication adherence has been related to the

frequency of use of intravenous antibiotics for exacerbation, and exacerbations have been associated with the failure to return to baseline pulmonary function (References 42, 103). Approaches to improve the adherence of individuals with CF include patient and caregiver education, with involvement by a child's school if needed, which should be provided at the start of care and reinforced with each clinic visit and inpatient admission. Interventions to improve adherence can be organizational (e.g., calendars, automated reminders by cell phone alarm), psychoeducational (e.g., reinforced education about disease, treatment, outcomes), or psychotherapeutic or motivational (e.g., therapy diary, setting goals). No single intervention is applicable to all, and because each patient is different, the choice of intervention approach should be a joint, patient-care team decision (Reference 104).

Approach to Caring for Patients with CF and the Role of the Pharmacist on Patient-Care Teams and in the Community

The treatment of individuals with CF is often approached in a systematic manner, involving the role of various health care providers including physicians, pharmacists, nurses, respiratory therapists, clinical nutritionists, clinical psychologists, physical therapists, and social workers. Information defining the role of a clinical pharmacy specialist in caring for patients with CF is limited, especially in the outpatient setting (e.g., CF centers). A survey of patients with CF conducted by European CF center investigators revealed that only 59% of patients reported access to specialty pharmacists (Reference 105). One of the first descriptions of pharmacist participation in the care of patients with CF described a role involving multidisciplinary rounds in the inpatient setting and the rotation of pharmacy residents in the CF clinic (Reference 106). Inpatient responsibilities of a pharmacist caring for patients with CF should include medication reconciliation, routine assessment of pharmacotherapy, communication with health care colleagues and families, and an active role in preparation for discharge, including home care (e.g., home intravenous antibiotics). Conversely, outpatient or ambulatory care setting responsibilities can include medication reconciliation, assessment of complementary and alternative therapy use, and assessment and intervention of medication adherence. Pharmacists in both inpatient and outpatient settings have a fundamental role in teaching patients and caregivers how to appropriately take or administer medications, including the timing of oral agents such as pancreatic enzymes and the use of metered dose inhalers and nebulized medications. Pharmacists can also play a central role in evaluating the use of dietary supplements, including complementary and alternative medications, because they may interact with prescribed drug therapy (Reference 107).

Interdisciplinary, family-centered care of patients with CF is a care model involving a variety of health care disciplines and has been an increasingly common practice in the inpatient setting. The central focus of this care model, patients and families play an important role in the successful, comprehensive care of patients with CF. Patients and caregivers are encouraged to participate in decision-making with respect to regimen design and approach to overall care. In fact, many CF centers have a family member serve as a representative of patients and families in a role noted as "family liaison." Pediatric Pulmonary Centers, supported by Maternal and Child Health Training grants, are an example of this patient-care model in the outpatient setting. These care centers involve teams composed of various disciplines including medicine, nursing, nutrition, respiratory therapy, social work, family liaisons or representatives, and, the most recent addition, pharmacy. As part of these programs, not only do the various disciplines work together to provide quality patient care to children, but they also provide a way of training future professionals (e.g., residents, interns).

With the complexity of CF drug therapy management given the challenging pharmacokinetics, the combination of acute and chronic drug therapies, and the diversity of patient ages and conditions secondary to medical advances, continuity of care is imperative to optimize medication efficacy while minimizing adverse drug events. A lack of data remains regarding the use and effect of a patient-care model that bridges specialist outpatient care to the management of acute exacerbations and continuation of clinically important maintenance drug therapy for hospitalized patients with CF. A model of continuity of care for these patients should possess elements of optimal drug therapy selection and consistency between outpatient and inpatient care involving an interdisciplinary approach. Additional investigation about effective combined care models will provide clinicians information regarding the active involvement of clinical pharmacy specialists as part of both the outpatient and inpatient care of patients with CF, thereby improving patient outcomes from drug therapy.

Pharmacists, as patient advocates, have a professional responsibility to undergo continued education and training about innovations in therapy to optimize the health of children and adults with CF. In addition to their role as health care providers, pharmacists can play a key role in clinical research, whether as principal investigator or collaborator. Studies of new agents, approaches to dosing, and innovations in therapy adherence interventions are a continued need for advancing patient care and improving quality of life. Advocacy as a clinician, researcher, educator, and/or community leader is a multifaceted role that pharmacists can play in the CF community—it is with this passion and dedication that the care of individuals with CF advances toward a future cure.

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PART III

FEN/Gastrointestinal

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Section Editor

CHAPTER 16

Gastroesophageal Reflux Disease

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Learning Objectives

1. Distinguish between the clinical presentations of gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) in pediatric patients.
2. Discuss treatment goals for the management of GER in pediatric patients.
3. List the risk factors for the development of severe, chronic GERD.
4. Discuss the role of both pharmacologic and nonpharmacologic treatment in the management of GER and GERD.
5. Recognize and manage common and potential adverse drug reactions with pharmacologic treatment of GER and GERD.

Abbreviations in This Chapter

ALTE	Apparent life-threatening event
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
H_2RA	Histamine-2 receptor antagonist
LES	Lower esophageal sphincter
PPI	Proton pump inhibitor
TLESR	Transient lower esophageal sphincter relaxation

Introduction

Gastroesophageal reflux (GER) is a common clinical manifestation in infancy and childhood. Gastroesophageal reflux disease (GERD) is a pathologic condition that may develop from reflux in patients of all ages. The first international consensus guideline on the diagnosis and management of GER and GERD in the pediatric population was recently published (Reference 1). The previous guideline published in 2001 included recommendations from only the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (Reference 2). These guidelines have changed the medical management of patients with GER and GERD.

Definitions

To better understand the disease process associated with reflux, several definitions are important. The first global, evidence-based consensus definition of GERD in the pediatric population was recently published (Reference 3). Gastroesophageal reflux is simply defined as the passage of stomach contents into the esophagus. It is a common occurrence in infancy and is not associated with any pathologic process, but it may be caused by food allergy or colic. Gastroesophageal reflux can manifest as spitting up or regurgitation. Regurgitation is defined as the passage of gastric contents into the oropharynx or mouth or possibly out of the mouth. Gastroesophageal reflux disease is defined as troublesome clinical symptoms and/or complications associated with the passage of stomach contents into the esophagus (Reference 3). Troublesome symptoms are those that affect a patient's quality of life such as heartburn, excessive regurgitation, food refusal, or abdominal pain. Complications of GERD are reflux esophagitis, hemorrhage, stricture, and Barrett esophagus (Reference 3). Reflux esophagitis is inflammation of the esophagus and the presence of damage to the esophageal mucosa (as erosions or ulcerations) as detected by biopsy. Barrett esophagus is a disorder in which the epithelial lining of the esophagus is replaced by epithelium similar to the stomach lining secondary to damage from acid reflux. Patients with this disorder are at high risk of developing esophageal adenocarcinoma. Gastroesophageal reflux disease can be associated with too much acid production, but it can also occur in children who present with no acid reflux. Nonerosive gastroesophageal disease is defined as the presence of typical symptoms of GERD without any erosive lesions within the esophagus.

GER in Infants

Epidemiology and Etiology

Gastroesophageal reflux is a normal physiologic process that occurs many times throughout the day in people of all ages. It is most common in infancy and usually resolves by 12–14 months of age (References 4, 5). Up to two-thirds of infants experience recurrent regurgitation and vomiting within the first 4 months of life, but only 5% of infants have symptoms of reflux beyond 1 year of age (Reference 6).

Physiologic reflux occurs when the lower esophageal sphincter (LES) relaxes and swallowing does not occur. This allows the passage of stomach contents into the esophagus. This can occur more often in neonates and infants because of the shorter length of the esophagus, delayed gastric emptying, decreased LES pressure, and immature peristalsis (Reference 7).

Gastroesophageal reflux can be associated with apnea, failure to thrive, and respiratory problems (recurrent aspiration, wheezing) in preterm infants. However, there is no evidence to suggest a causal relationship between GER and these occurrences. One study evaluating the prevalence of infant regurgitation in infants younger than 2 years found no difference in GER between preterm and term infants (Reference 6).

Clinical Presentation and Diagnosis

The most common symptom associated with physiologic reflux in the infant is regurgitation or "spitting up." Reflux can also trigger vomiting. Other signs and symptoms that can be associated with reflux are nonspecific and include irritability, excessive crying, lethargy, feeding refusal, and cough (Table 1). These cannot be distinguished from other causes of reflux such as food allergy or colic. Infants with uncomplicated physiologic reflux are commonly referred to as "happy spitters." These infants can continue to gain adequate weight despite the problematic symptoms associated with reflux.

Reflux episodes can have a temporal relationship with apnea; however, evidence is conflicting whether there is a temporal or causal relationship between apnea and reflux (Reference 1). Apparent life-threatening events (ALTEs) are episodes of sustained apnea, cyanosis, abnormal muscle tone, and gagging that usually occur in the first 3 months of life. They are frightening episodes for parents or caregivers that usually result in admission to the hospital for further diagnostic evaluation. An ALTE may be associated with reflux in an infant; however, ALTEs are not thought to be caused by GER (Reference 1).

The diagnosis of physiologic reflux is often based solely on the parental history and physical examination. Clinicians should perform a thorough examination of the child and obtain a detailed feeding history and description of the exact symptoms, including when they occur in relation to feeding. In addition, a thorough medical and family history should be obtained, including a family history of reflux and other gastrointestinal disorders (celiac disease, *Helicobacter pylori* infection). Invasive testing is not usually required unless there is a suggestion of another pathologic diagnosis including GERD.

The I-GERQ-R (Infant Gastroesophageal Reflux Questionnaire Revised) is a validated diagnostic questionnaire composed of 14 items that can be used to guide clinicians when obtaining a history, and it has also been found to help monitor symptom occurrence with time (Reference 8). The items are questions related to the characteristics of regurgitation, crying, feeding refusal, apnea or cyanosis, hiccups, and abnormal body posturing. The Rome III criteria were established to provide diagnostic criteria for infant regurgitation and other functional gastrointestinal disorders. Healthy infants who are 3 weeks to 12 months of age must present with both of the following: (1) regurgitation 2 or more times per day for 3 or more weeks and (2) no retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing to be diagnosed with infant regurgitation (Reference 9).

Table 1. Signs and Symptoms Suggestive of GER

Age group	Infants < 1 year	Children 1–5 years old	Older children and adolescents (6–17 years old)
Symptoms	Regurgitation Vomiting Arching Irritability Poor weight gain Crying	Regurgitation Abdominal pain Cough	Heartburn Epigastric pain Dysphagia
Signs	Sandifer syndrome Food refusal Failure to thrive ALTE	Food refusal Recurrent pneumonia Dental erosions	Reflux esophagitis

ALTE = apparent life-threatening event; GER = gastroesophageal reflux.
Adapted from Reference 1.

All infants who present with extraesophageal symptoms (apnea, ALTE, arching of the back, failure to thrive) and/or bilious vomiting should undergo a further diagnostic workup. Extraesophageal symptoms are commonly associated with GERD. Bilious vomiting is usually indicative of an obstruction or pyloric stenosis.

Prognosis

Most infants with physiologic reflux have a favorable prognosis because they "outgrow" the symptoms by 1 year of age. Children who have persistent symptoms beyond 18 months of age, neurologic impairment, prematurity, or a strong family history of GERD have a worse prognosis compared with infants who have physiologic reflux.

Treatment

The goals of therapy are to provide parental reassurance and education, alleviate patient symptoms, and prevent complications. The mainstay of treatment in GER is nonpharmacologic. Management strategies include lifestyle changes (feeding and positional changes) and dietary changes. Pharmacologic management is reserved for the management of GERD.

Nonpharmacologic Therapy

Lifestyle Modifications

Lifestyle modifications for infants with physiologic GER include parental reassurance, positional changes, and dietary changes (Box 1). Parental education should include counseling on the management of GER when it occurs, the prevention of reflux episodes, and the natural course and duration of infantile physiologic reflux, as well as counseling on when to seek additional treatment if symptoms persist or complications are noted. Parents should also be counseled on different positioning during and after feeding, burping, and other techniques to reduce the likelihood of reflux episodes.

In infants, the supine position is preferred to the prone position for sleeping. Despite studies showing the prone position can lessen reflux episodes, a significantly increased risk of sudden infant death syndrome exists compared with the supine position (References 10, 11). For this reason, the prone position is only acceptable when infants are awake and carefully watched after a meal. In addition, holding a sleeping infant in an upright position for the first 20–30 minutes after feeding if they are asleep is acceptable (Reference 1).

Dietary Changes

Potential dietary changes include changing the volume or frequency of feeding, trying a hypoallergenic or antireflux formula, and thickening the formula to increase caloric density. One of the most common situations discovered upon questioning parents and caregivers about reflux and regurgitation in their infant is overfeeding. Altering the feeding volume and frequency can be beneficial to infants with GER. Studies have shown that smaller-volume feeds can decrease acid reflux (Reference 12). However, clinicians should be cautioned that decreasing the volume or frequency of feeds may lead to inadequate weight gain.

The most common practice when changing the feeding volume is also to add a thickening agent, which will increase the caloric content of the formula. This is done to ensure adequate weight gain in the infant. Rice cereal is the most common thickening agent used. One tablespoon of rice cereal per 2 oz increases the formula from 20 calories per ounce to 27 calories per ounce (Reference 1). The addition of rice cereal does not change the amount of acid reflux, but it does decrease the amount of regurgitation (References 13, 14). The potential disadvantages of adding rice cereal to formula include increased coughing during feeding and the extra energy expenditure in the infant because of the increased viscosity of the formula (Reference 15). If infants have to suck a thicker substance through the nipple in the bottle, they will use more energy during the feeding process, which can cause an increase in caloric requirements. Infants typically need an enlarged nipple for adequate sucking when using a thickened formula.

Prethickened, anti-regurgitation (AR) formulas are commercially available. These formulas include the addition of starch, which thickens only when mixed with the acid in the stomach. These formulas, which do not require the addition of an enlarged nipple, have been found to decrease both the amount of regurgitation and the amount of acid reflux (Reference 16). Theoretically, there is a potential drug interaction with AR formulas

Box 1. Lifestyle changes for patients with GER and GERD.

- Infants
  - Parental reassurance
  - Dietary changes
  - Positional changes
- Older children and adolescents
  - Dietary changes
  - Sleeping position changes
    - Elevate head of bed.
    - Left-sided sleep position
  - Weight loss
  - Decreased tobacco smoke exposure

GER = gastroesophageal reflux; GERD = gastroesophageal reflux disease.

and histamine-2 receptor antagonists (H_2RAs). Because acid content in the stomach is required for the formula to work, there may be a decreased effect of the AR formula in a patient also taking a histamine receptor antagonist. Although this interaction has only been reported with the H_2RAs, it could theoretically occur with a proton pump inhibitor (PPI) as well. It is recommended to have a trial of AR formula first in an infant with GER before initiating any acid suppression therapy.

Because it is difficult to distinguish between infants with reflux and those with a milk protein allergy, changing to a hypoallergenic formula may prove beneficial in many patients. Trials of feeding with either protein hydrolysate or amino acid formulas for infants having regurgitation longer than 4 weeks have been successful in decreasing vomiting and are recommended according to the current guidelines (Reference 17). However, there is no evidence for soy formula in the management of infant reflux (Reference 1).

Gastroesophageal Reflux Disease

Epidemiology and Etiology

The prevalence of GERD has increased during the past several years in both adults and children. The true prevalence in pediatric patients is unknown because of the lack of a consistent definition used in practice. In addition, both the prevalence and incidence vary among the different age groups (neonates, infants, children, and adolescents). The prevalence is highest in infants younger than 1 year (Reference 18). The incidence of GERD ranges from 5% to 35% (Reference 19). Males are affected more than females. Bottle-fed infants are at an increased risk of GERD compared with breastfed infants.

More than one-half of the pediatric patients who are given a diagnosis of GERD require medical management of their disease. In one study, 4% of all hospital admissions annually were because of GERD (Reference 20). In addition, it is estimated that $750 million are spent annually on the management of childhood GERD in hospitals (Reference 20).

Pathophysiology

Gastroesophageal reflux disease is caused by transient lower esophageal sphincter relaxations (TLESRs), decreased LES pressure, delayed gastric emptying, and hiatal hernia.

The movement of reflux from the stomach into the esophagus usually occurs during TLESRs. Normally, the LES relaxes very briefly (3–10 seconds) in response to swallowing. Transient lower esophageal sphincter relaxations occur when the LES relaxes for more than 10 seconds and is not induced by the swallowing mechanism. Reflux episodes can also occur because of decreased LES pressure or inability of the LES to increase in response to increased intra-abdominal pressure. Factors that can contribute to decreased LES pressure include tobacco smoke exposure, intake of fatty foods, certain medications (theophylline, calcium channel blockers), and gastric distention. In addition, normal digestive defense mechanisms can become impaired in the presence of acid reflux and further exacerbate GERD symptoms. Continued exposure of the mucosa and submucosa within the esophagus to refluxate, primarily containing acid, can lead to the development of erosions in the esophagus.

Genetic Basis

Evidence suggests that GERD has a genetic component. A specific locus on chromosome 13 (13q14) associated with severe pediatric GERD has been identified (Reference 21). In addition, there are reports of a familial association with GERD. Reflux symptoms, hiatal hernia, erosive esophagitis, Barrett esophagus, and esophageal adenocarcinoma occur more commonly within families (References 22, 23).

Risk Factors

There are several pediatric patient populations that are at increased risk of severe, chronic GERD and complications associated with GERD. These include neurologic impairment (e.g., cerebral palsy), obesity, esophageal atresia, chronic lung disease, and prematurity. These patient populations have a poor prognosis and require long-term treatment of the symptoms associated with GERD (Reference 1).

Clinical Presentation

The troublesome signs and symptoms associated with GERD include vomiting, irritability, refusal to feed, heartburn, dysphagia, and Sandifer syndrome. Sandifer syndrome is defined as spasmodic dystonia with arching of the neck and back and abnormal posturing (Reference 3). It is important to distinguish between this clinical presentation and similar movements that may be caused by seizures or infantile spasms. Table 1 lists the most common signs and symptoms seen according to age group.

Gastroesophageal reflux disease may or may not lead to erosive esophagitis. This is because GERD can be caused by both acid and nonacid reflux. Symptoms most commonly associated with nonacid reflux include regurgitation and cough. Patients with erosive esophagitis typically present with heartburn and belching.

Gastroesophageal reflux disease is associated with both esophageal and extraesophageal symptoms. The most common extraesophageal symptoms in children include respiratory symptoms such as apnea, coughing,

and wheezing. Extraesophageal manifestations of GERD include asthma, pneumonia, nocturnal cough, sinusitis, laryngitis, otitis media, and dental erosions. New or expanded sections about the clinical presentation and treatment of certain high-risk populations appear in the new guideline, including neurologic impairment (anoxic brain injury, cerebral palsy, Down syndrome), obesity, esophageal anatomic disorders, chronic respiratory disorders (cystic fibrosis, bronchopulmonary dysplasia), lung transplantation, and prematurity (Reference 1).

Diagnosis

An initial diagnosis of GERD is often based on the clinical presentation of the patient with typical signs or symptoms for reflux. However, because many of the signs and symptoms are nonspecific (weight loss, dysphagia, cough, irritability), it is difficult to rely only on the clinical presentation for a diagnosis. Other disease states cannot be ruled out on the basis of clinical presentation alone. In addition, children younger than 8–12 years cannot reliably report their subjective symptoms, and children who are unable to communicate (e.g., those with neurologic impairment) will not be able to provide a description of their symptoms (Reference 1). Adolescents who present with typical heartburn symptoms can be given a diagnosis on the basis of symptoms alone, similar to adult patients (Reference 1). This is only applicable to adolescents who are verbal and neurologically intact.

Patients with suspected GERD should undergo a thorough history and physical examination to determine the timing and severity of symptoms and to ascertain whether any complications are present that require further evaluation. Questions should be asked about the feeding history and vomiting, as well as the social, medical, family, and medication history (Reference 24). The history and physical examination can also be used to rule out other disease states such as pyloric stenosis or seizures. Diagnostic questionnaires, such as those previously mentioned for GER, are also helpful for monitoring of symptoms. Unfortunately, there is a poor correlation between symptoms and objective findings in patients with GERD (References 25, 26).

Many diagnostic tests can be used to aid in the diagnosis of GERD. Esophageal pH monitoring involves placing a catheter with electrodes along the length through the nose to the LES to measure the frequency and duration of acid reflux episodes (Reference 27). Recordings of the number and frequency of episodes are completed during a 24-hour period. Esophageal pH monitoring alone is not sensitive for the detection of nonacid or weak acid reflux. Normal esophageal pH is 7.0. Acid reflux is defined as an esophageal pH less than 4.0 lasting 15–30 seconds (Reference 28). The most reliable marker used during pH monitoring is the reflux index (RI) score. The RI is defined as the percentage of total time that the esophageal pH is less than 4.0. A score greater than 7% is considered abnormal for all patients older than 1 year and 12% or more in infants (References 1, 29). Additional parameters measured by this procedure include the total number of reflux episodes, episodes lasting more than 5 minutes, and duration of pH less than 4.0. Combining pH monitoring with multiple intraluminal impedance allows the type of reflux to be detected: gas, liquid, solid, or mixed. Thus, it can detect weakly acidic and basic reflux episodes. In addition, it detects the volume and direction of the reflux.

An upper gastrointestinal endoscopy allows visualization and evaluation of the esophageal mucosa. This test is useful to determine the presence of esophagitis and complications of GERD such as strictures, hiatal hernia, ulcers, or Barrett esophagus. Biopsies of the mucosa should be obtained during the procedure to evaluate histologic changes in the mucosa. The biopsy can also be used to determine whether there are eosinophils in the tissue, which is consistent with a diagnosis of eosinophilic esophagitis, an allergic inflammatory disorder of the esophagus.

The upper gastrointestinal series is a procedure that uses barium contrast radiography to evaluate the upper gastrointestinal tract. This procedure is not specific or sensitive for GERD, but it can be useful in identifying malrotation, pyloric stenosis, hiatal hernia, and anatomic abnormalities such as tracheoesophageal fistula (Reference 30). These diagnoses may also be considered in pediatric patients with symptoms similar to GERD.

Esophageal manometry measures peristalsis, upper and LES pressures, and coordination of swallowing with these functions. Unfortunately, GERD cannot be diagnosed by manometry because of its low sensitivity and specificity (Reference 1). Instead, manometry is used to determine the presence of motility disorders that may have a clinical presentation similar to GERD.

A trial of acid suppression is no longer recommended for infants and young children as a diagnostic test (Reference 1). Older children and adolescents can still have a 2- to 4-week trial to determine whether therapy is beneficial.

Treatment

The goals of therapy are to alleviate patient symptoms, heal esophagitis if present, maintain normal growth, prevent complications, and minimize adverse effects of drug therapy. These goals are accomplished with nonpharmacologic interventions such as lifestyle modifications and pharmacologic interventions with acid suppression therapy.

Nonpharmacologic Therapy

Nonpharmacologic therapies include lifestyle modifications and antireflux surgery. Specific lifestyle modifications are listed in Box 1. Mild symptoms of GERD without complications may be managed by lifestyle changes alone. Strategies for infants include those previously discussed for GER. In rare cases, particularly for patients with recurrent pneumonia and GERD, placement of a nasogastric or nasojejunal feeding tube is required to ensure adequate feeding and growth and to prevent aspiration (References 31, 32). Older children and adolescents should be encouraged to avoid the ingestion of large meals, as well as to avoid lying down immediately after eating a meal. They should also avoid foods that may exacerbate reflux symptoms such as caffeine, chocolate, and spicy foods. Of importance, the effectiveness of specific lifestyle modifications, such as positioning during sleep, has not been studied in children and adolescents; rather, data have been extrapolated from adult studies. In adults, only weight loss has been shown to improve pH profiles and symptoms. Studies have shown that elevating the head of the bed in adults is beneficial (fewer episodes of reflux), so older children and adolescents may also benefit as well. Data on the additive benefit of lifestyle changes to pharmacologic therapy are also lacking for children and adolescents (Reference 1).

Antireflux surgery is recommended only for specific patients: (1) children with GERD whose optimal medical therapy fails, (2) patients with a requirement for long-term medical therapy when adherence or patient preference impedes such use, and (3) patients with life-threatening complications (chronic aspiration, respiratory symptoms, or Barrett esophagus) (Reference 1). The most common surgical procedure is the Nissen fundoplication. This procedure can be performed laparoscopically or as an open surgery, with the laparoscopic procedure preferred. The fundus of the stomach is wrapped 360 degrees around the lower end of the esophagus and stitched in place to serve as the closure for the LES. This results in increased LES pressure and a decreased number of TLESRs. Surgery can be curative in a subset of patients; however, success rates vary greatly from about 60% to 90% (Reference 33). Complications after surgery can include gas-bloat syndrome, dysphagia, diarrhea, and retching and gagging after feeding. Patients with neurologic impairment are at highest risk of complications after antireflux surgery. In fact, patients with neurologic impairment have twice the postoperative complication rate, a 3-fold higher morbidity (return to preoperative symptoms), and a 4-fold higher reoperation rate compared with patients who are neurologically intact (Reference 34).

A recent study found a decrease in reflux-related hospitalizations (aspiration pneumonia, pneumonia, esophagitis, esophageal reflux) in patients who received antireflux surgery at younger than 4 years, but no benefit in older children and an increase in hospitalizations in those older than 4 years with developmental delay (Reference 35). The risks and benefits of antireflux surgery should be carefully considered before recommending this as a treatment option.

Pharmacotherapy

Pharmacotherapeutic options for the management of GERD in pediatric patients include gastric acid–suppressing agents, mucosal surface barriers, and prokinetic agents. The H_2RAs and PPIs are considered first-line therapy for managing GERD in pediatric patients. The role of antacids and prokinetic agents will also be discussed. Table 2 lists pharmacologic agents used in the management of pediatric GERD, including their advantages, disadvantages, and specific place in therapy. Table 3 includes information on the specific dosing and formulations of various products.

Histamine-2 Receptor Antagonists

The H_2RAs decrease acid production by competitive inhibition of the histamine-2 receptors in gastric parietal cells. They do not inhibit meal-stimulated acid secretion. The H_2RAs are most effective for the on-demand relief of GERD symptoms and cases of mild esophagitis. The H_2RAs are less effective than the PPIs for symptom relief and healing of esophagitis (Reference 1). Symptomatic improvement is seen in 70% of patients 1 to 18 years of age, and endoscopic healing rates are reported to be between 50% and 95% in infants and children > 1 month (References 36, 37). One case series in infants 72 hours to 16 years of age, found endoscopic healing rates of 95% with the use of ranitidine (Reference 38). Although H_2RAs are commonly prescribed in neonates and preterm infants, there are limited efficacy and safety data available for these patients (References 1, 39, 40). Studies have been conducted suggesting an association with H_2RAs and the development of necrotizing enterocolitis in preterm infants (Reference 41).

Drugs in this class include ranitidine, famotidine, nizatidine, and cimetidine. Ranitidine is the most widely used agent because it is well tolerated, with a low potential for drug interactions. Cimetidine is rarely used because of the high incidence of adverse effects such as gynecomastia, increased risk of liver disease, neutropenia, and thrombocytopenia and because it inhibits cytochrome P450 (CYP), which can lead to significant drug interactions. The H_2RAs achieve peak plasma concentrations within 2.5 hours, and the duration of acid suppression is 6 hours (Reference 42). This necessitates

Table 2. Therapeutic Management of Pediatric GERD

Pharmacologic Class	Advantages	Disadvantages	Specific Place in Therapy
H_2RAs	▪ Quick onset of acid inhibition and symptom relief ▪ Data to support use in pediatric patients ▪ Cost-effective ▪ No need to taper upon discontinuation ▪ Availability of liquid formulations	▪ Tolerance ▪ Adverse effects	▪ On-demand therapy ▪ Maintenance therapy for mild GERD or esophagitis
PPIs	▪ Most potent acid suppression ▪ Inhibition of meal-induced acid secretion ▪ Greater efficacy than H_2RAs in healing esophagitis	▪ Limited formulations available for pediatric patients ▪ CYP genetic polymorphisms ▪ Adverse effects ▪ Cost ▪ Risk of increased community-acquired pneumonia and *Clostridium difficile*–associated diarrhea	▪ First-line maintenance therapy for GERD ▪ First-line initial management of erosive esophagitis for 3 months (mild to severe)
Prokinetic agents	▪ Facilitate gastric emptying ▪ Symptomatic improvement	▪ Significant adverse effects ▪ Inferior efficacy to PPIs and H_2RAs ▪ Limited clinical evidence (with exception of metoclopramide)	▪ Routine use not recommended ▪ May be useful in patients with delayed gastric emptying in combination with an H_2RA or PPI
Antacids	▪ Quick onset ▪ Variety of dosage forms available ▪ Low risk of adverse effects	▪ Require frequent administration ▪ Inferior efficacy to PPIs and H_2RAs	▪ On-demand therapy in patients maintained on H_2RAs or PPIs
Surface agents	▪ Form a protective coat that may aid in mucosal healing ▪ Low risk of adverse effects	▪ Limited clinical evidence	▪ Adjunctive therapy for erosive esophagitis with H_2RAs or PPIs

CYP = cytochrome P450; GERD = gastroesophageal reflux disease; H_2RA = histamine-2 receptor antagonist; PPI = proton pump inhibitor.
Adapted from Reference 1.

dosing two or three times/day. Infants usually require thrice-daily dosing because the gastric pH decreases within 5 hours (Reference 17). One study showed that higher doses of ranitidine (20 mg/kg/day compared with 8 mg/kg/day) were as efficacious as omeprazole (Reference 43).

The H_2RAs are associated with some adverse effects, such as irritability, headache, and somnolence in infants. These effects could be mistaken for continual symptoms of GERD in some patients. Tolerance of the acid-suppressive effect of the H_2RAs can develop after 6 weeks of therapy (References 44, 45). This phenomenon is not overcome by a dosage increase (Reference 45).

Proton Pump Inhibitors

The PPIs inhibit both basal and meal-induced acid secretion by inactivating the H^+/K^+-ATPase pump in parietal cells (the proton pump). This pump acts as the parietal cell membrane transporter. The PPIs irreversibly inhibit the pump; thus, acid secretion can only return once the parietal cell makes new pumps. The PPIs have also been shown to decrease 24-hour intragastric volumes, which helps facilitate gastric emptying and decrease the volume of reflux (Reference 46). The PPIs have superior efficacy to the H_2RAs because they have a longer duration of action for acid suppression,

Table 3. Pediatric Doses of Medications Used in the Management of GERD

Agent	Dose (Oral)	Formulations
	H_2RAs	
Ranitidine (Zantac)	Neonates: 2 mg/kg/day divided q12h Infants, children, adolescents: 4–10 mg/kg/day divided bid-tid (max: 300 mg/day; 600 mg/day if erosive esophagitis)	15 mg/mL syrup 75-, 150-, 300-mg tablet 150-, 300-mg capsule 25-mg effervescent tablet for solution
Famotidine (Pepcid)	Neonates to 3 months: 0.5 mg/kg/day once daily ≥ 3 months to 12 years: 1 mg/kg/day divided bid (max: 80 mg/day) > 12–18 years: 20 mg bid (GERD) 10–20 mg before meals (heartburn)	40 mg/5 mL powder for suspension 10-, 20-, 40-mg tablet 20-mg chewable tablet
Cimetidine (Tagamet)	Neonates: 5–10 mg/kg/day divided bid-tid Infants: 10–20 mg/kg/day divided bid-qid Children/Adolescents: 20–40 mg/kg/day divided qid (max 1600 mg/day)	300 mg/5 mL solution 200-, 300-, 400-, 800-mg tablet
Nizatidine (Axid)	6 months to 11 years: 5–10 mg/kg/day divided bid ≥ 12 years: 150 mg bid	15 mg/mL solution 150-, 300-mg capsule
	PPIs	
Omeprazole (Prilosec)	Infants < 1 year: 0.7–1.5 mg/kg/day once daily 1–16 years: 5 kg to < 10 kg: 5 mg/day 10 kg to ≤ 20 kg: 10 mg/day > 20 kg: 20 mg/day Alternative: 1 mg/kg/day (range, 0.2–3.5 mg/kg/day) given qday or bid	10-, 20-, 40-mg delayed-release capsule 20-mg delayed-release tablet 2.5-mg granules for oral suspension packet Extemporaneous suspension formula available
Omeprazole and sodium bicarbonate (Zegerid)	Same as omeprazole	20-, 40-mg immediate-release capsule (contains 1100 mg sodium bicarbonate) 20-, 40-mg of powder for oral suspension packet (contains 1680 mg sodium bicarbonate per packet)
Esomeprazole (Nexium)	Neonates: 0.5 mg/kg/day once daily × 7 days Infants 1–24 months: 0.25–1 mg/kg/day once daily 1–11 years: < 20 kg: 10 mg/day for 8 weeks > 20 kg: 10–20 mg/day for 8 weeks 12–17 years: 20–40 mg/day for 8 weeks	20-, 40-mg delayed-release capsule 10-, 20-, 40-mg granules for suspension packet 20-, 40-mg injection

Agent	Dose (Oral)	Formulations
Lansoprazole (Prevacid)	Neonates: 0.2–1 mg/kg/day once daily Infants: < 10 weeks: 0.2–0.3 mg/kg/day ≥ 10 weeks: 1–2 mg/kg/day once daily 1–11 years: ≤ 30 kg: 15 mg/day > 30 kg: 30 mg/day ≥ 12 years: 15 mg/day (erosive esophagitis: 30–60 mg/day)	15-, 30-mg delayed-release capsule 15-, 30-mg orally disintegrating tablet 15-mg 24-hour tablet Extemporaneous suspension formula available
Dexlansoprazole (Dexilant)	Not recommended for patients < 18 years Adults: GERD: 30 mg/day for 4 weeks Erosive esophagitis: 60 mg/day for 8 weeks; then 30 mg/day for 6 months	30-, 60-mg delayed-release capsule
Pantoprazole (Protonix)	Erosive esophagitis: 15 kg to < 40 kg: 20 mg/day (alternative: 0.5–1 mg/kg/day) ≥ 40 kg: 40 mg/day	20-, 40-mg delayed-release tablet 40-mg granules for suspension 40-mg injection
Rabeprazole (AcipHex)	≥ 12 years: 20 mg/day for 8 weeks	20-mg delayed-release tablet
	Prokinetic Agents	
Metoclopramide (Reglan)	Neonates: 0.1–0.15 mg/kg/dose q6h Infants, children, adolescents: 0.4–0.8 mg/kg/day divided qid (max 60 mg/day)	5 mg/5 mL solution 5-, 10-mg tablet
Erythromycin	Infants: 0.75–3 mg/kg/dose q8h (up to 10 mg/kg/dose) Children and adolescents: 10–20 mg/kg/day divided bid-qid before meals (max: 250 mg tid)	200 mg/5 mL, 400 mg/5 mL powder for suspension 250-mg delayed-release capsule 250-, 500-mg tablet 400-mg tablet (as ethylsuccinate) 250-, 333-, 500-mg delayed-release, enteric-coated tablet
Bethanechol	Children: 0.4–0.8 mg/kg/day divided qid	5-, 10-, 25-, 50-mg tablet Extemporaneous suspension formula available

bid = two times/day; GERD = gastroesophageal reflux disease; h = hour; q = every; qid = four times/day; tid = three times/day.
Lexicomp. Available at http://online.lexi.com/crlsql/servlet/crlonline. Accessed September 16, 2011.

inhibit meal-induced acid secretion, and are not associated with the development of tolerance. Drugs in this class include omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole.

The PPIs are first-line therapy for the management of chronic heartburn in older children and adolescents, reflux esophagitis in infants and children, and on-demand relief of GERD-related symptoms. For the older child or adolescent with heartburn, a 2- to 4-week diagnostic trial of a PPI (in addition to lifestyle changes) is recommended to determine whether an improvement in symptoms occurs. If there is improvement, the PPI can be continued for 8–12 weeks. In the management of reflux esophagitis, PPIs produce mucosal healing in 70% to 100% of patients within 12 weeks and symptom improvement in up to 80% of patients (References 47–49). They have also been shown to heal more severe grades of esophagitis and cases refractory to H_2RAs. For erosive esophagitis, initial treatment should be continued for 12 weeks.

Currently, only esomeprazole has an FDA indication for use in children younger than 1 year. However, off-label use of PPIs in infants younger than 1 year is quite common. The prevalence of PPI use is increasing

among pediatric patients. A 2004 study showed an 11-fold increase in PPI use among infants younger than 12 months during a 6-year period and a shift from omeprazole to lansoprazole as the most commonly prescribed PPI (Reference 50). Evidence exists describing the pharmacokinetics, pharmacodynamics, efficacy, and safety in this age group for both omeprazole and lansoprazole. However, at present, the efficacy data do not support the routine use of PPIs in children younger than 1 year, and concerns have been raised about the safety of these agents in this age group (References 1, 51).

Omeprazole is the most widely studied PPI in pediatric patients. Data support both its efficacy and long-term safety. Until 2004, it was also the most widely prescribed PPI, used in almost 90% of pediatric patients (Reference 52). Since then, lansoprazole has become the most commonly prescribed PPI in pediatric patients (65%), followed by omeprazole (20%), pantoprazole (7%), esomeprazole (5%), and rabeprazole (less than 1%) (Reference 53).

Pantoprazole has been studied in patients 5–18 years of age for both GERD-related symptoms and reflux esophagitis, with healing rates similar to other PPIs (80% to 90%) (Reference 54). Esomeprazole has been studied in all pediatric age groups (including preterm infants), and it has been found both safe and efficacious. Researchers have also found similar age-related pharmacokinetics in metabolism and elimination compared with omeprazole and lansoprazole. Rabeprazole has been studied in adolescents 12–16 years of age, and studies are under way to evaluate its use in younger patients (Reference 55). Rabeprazole has been found to be well tolerated in adolescents at 10- and 20-mg doses. Accumulation of the drug occurred with repeated administrations of the 20-mg dose. Further investigation into the significance of this phenomenon was recommended.

The proton pumps are most active when stimulated by a meal, so the ideal time to take a PPI is 15–30 minutes before the first meal of the day. Because these agents are broken down by gastric acid, most formulations are enteric coated and delayed release. Administration of delayed-release capsules is challenging in infants and young children. No liquid formulations are commercially available, but extemporaneous preparations of lansoprazole and omeprazole have been made using sodium bicarbonate. In addition, immediate-release orally disintegrating tablets of lansoprazole are available. The PPIs have a delayed onset of action of up to 4 days (Reference 1). Once administered, the PPI can continue to inhibit acid secretion for up to 15 hours, requiring only one dose per day in most patients (Reference 56). Despite this, some patients continue to experience heartburn of less severity and may even experience nocturnal acid breakthrough (gastric pH of less than 4.0 for more than 1 hour within 12 hours of a PPI dose) (Reference 57).

Pharmacokinetic data show that children 1–10 years of age require a higher milligram-per-kilogram dose than adolescents and adults. In addition, infants may require lower milligram-per-kilogram dosing than children and adolescents (Reference 1). A recent study with lansoprazole found that infants 10 weeks and younger had higher plasma concentrations and lower clearance compared with infants older than 10 weeks to 1 year. Thus, a lower dose of lansoprazole is recommended in patients 10 weeks or younger (Reference 51).

The PPIs are metabolized by CYP 2C19 and 3A4. The enzymatic activity of 2C19 varies with age. Low at birth, 2C19 enzymatic activity reaches adult values at 6–12 months of age, exceeds adult values between 1 and 4 years of age, and then decreases back to adult levels around puberty (Reference 58). This explains differences in the metabolism and clearance of PPIs among various age groups. There is evidence of reduced metabolism in neonates and preterm infants and increased clearance in children compared with adults. Polymorphisms also exist for CYP2C19 with three phenotypes: homozygous extensive metabolizers, heterozygous extensive metabolizers, and poor metabolizers. When dosing PPIs in pediatric patients, consider interindividual variability caused by the pharmacokinetic and pharmacodynamic relationships that exist, particularly with metabolism and elimination (Reference 59). Rabeprazole metabolism does not appear to be as affected as other PPIs by alterations in the CYP2C19 genetic polymorphisms. This is because rabeprazole undergoes some nonenzymatic metabolism. PPIs decrease the absorption of drugs requiring an acidic environment to be absorbed. Drugs that may be affected include itraconazole and griseofulvin. Omeprazole has also been associated with decreased clearance of diazepam and carbamazepine because of its inhibition of CYP2C19 (References 60, 61). Close monitoring of carbamazepine levels is required when coadministered with omeprazole.

Common adverse effects of PPIs include headache, nausea, constipation, and diarrhea. It is recommended to change to a different agent or decrease the dose if any of these adverse effects occur (Reference 1). The PPIs can also be associated with some severe adverse effects, including acute interstitial nephritis, parietal cell hyperplasia, fundic gland polyps, enterochromaffin cell-like hyperplasia, vitamin B_{12} deficiency, and bone loss. These severe effects have been reported more often in patients on prolonged therapy (greater than 2 years) and in adult patients. Because there is a possibility of rebound acid secretion upon PPI discontinuation, the guidelines suggest that PPIs be tapered off over 4 weeks when therapy is complete. However, the evidence supporting this practice is conflicting (Reference 1).

Long-term acid suppression is not without complications. Gastric acid is protective to the digestive system because it inhibits bacterial flora. Bacterial overgrowth can occur in patients taking gastric acid inhibitors. Both H_2RAs and PPIs have been found to increase the rates of (1) community-acquired pneumonia in children, (2) acute gastroenteritis in children, (3) necrotizing enterocolitis in premature infants, (4) candidemia in premature infants, and (5) *Clostridium difficile*–associated diarrhea in children (References 62–64).

Prokinetic Agents

Prokinetic therapy used for the management of GERD in pediatric patients includes metoclopramide, erythromycin, bethanechol, and baclofen. A recent systematic review of healthy children 1 month to 2 years of age with GER found that metoclopramide produces modest decreases in daily symptoms but is associated with considerable adverse effects (Reference 65). Serious adverse effects of metoclopramide include extrapyramidal reactions and tardive dyskinesia. Erythromycin has been used to increase gastric emptying in some patients because of its action on motilin, but there is limited evidence on its use in GERD. The dose for its prokinetic activity is less than that for the treatment of bacteria; thus, adverse effects are rare at these lower doses. However, there is still a slight risk of gastrointestinal upset, hepatotoxicity, arrhythmias, and antibiotic resistance with erythromycin use. Bethanechol, a direct cholinergic agonist, has uncertain efficacy and unwanted adverse effects (headache, malaise, abdominal cramps, belching, nausea, vomiting). Baclofen works to decrease TLESRs and can increase gastric emptying. Baclofen has been found efficacious in reducing vomiting in children with neurologic impairment and GERD. Because baclofen works directly on the central nervous system, there is a high incidence of adverse effects, such as somnolence, headache, insomnia, and confusion (Reference 66). From the available evidence, the routine use of prokinetic agents for GERD is not recommended. Despite the lack of evidence supporting its efficacy, metoclopramide is still the most widely used prokinetic agent in the pediatric population for the management of GERD (Reference 1).

Antacids

Antacids work by buffering gastric acid within the stomach and esophagus, thereby facilitating mucosal healing. Antacid therapy (magnesium hydroxide, aluminum hydroxide, calcium carbonate) is recommended for on-demand relief of heartburn in older children and adolescents. The advantage to antacid therapy is its quick onset of action, but because of its short half-life, frequent administration is required. All antacids should be used with caution in infants and young children because they increase plasma aluminum levels and can cause milk-alkali syndrome, a condition associated with hypercalcemia, alkalosis, and renal failure. Chronic antacid therapy for pediatric GERD is not recommended because more effective agents are available (Reference 1).

Surface-Protective Agents

Surface-protective agents contain either sucralfate or alginate. Sucralfate is a mixture of sucrose, sulfate, and aluminum. In an acidic environment, sucralfate forms a gel that coats the mucosal surface. Alginate alone is useful for on-demand therapy. The commercially available product for infants and young children contains only sodium and magnesium alginate. Older children and adolescents may take the adult formulation that contains both alginate and the buffering agents found in antacids. Surface-protective agents are only recommended as adjunctive therapy for the management of esophagitis and severe GERD-related symptoms. They can be used for on-demand therapy in patients with bothersome symptoms despite maximal doses of PPIs, but they are not recommended for chronic therapy (Reference 1).

Combination Therapy

Recommendations on the use of combination therapy are unavailable in current guidelines (Reference 1). The most common combination of medication classes is an H_2RA or PPI with a prokinetic agent or an H_2RA and a PPI. In general, changing to a different agent is preferred to adding another agent for chronic maintenance therapy. With multiple agents, there is a potential for increased adverse effects. In addition, H_2RAs and PPIs have a theoretical antagonistic mechanism of action because PPIs require the presence of acid to inhibit proton pumps, and H_2RAs directly inhibit acid production. Twice-daily dosing of both an H_2RA and PPI would provide potent acid suppression but could further increase the risk of respiratory infections or gastroenteritis.

Adult patients with nocturnal acid breakthrough on PPIs have decreased symptoms with the addition of a bedtime dose of an H_2RA, suggesting that nocturnal acid breakthrough is histamine-related. However, the effect is not lasting secondary to the tolerance that develops to H_2RAs. In children, the data are limited to one small study (18 children: 1–13 years), which showed no benefit to this strategy (Reference 67). Therefore, adding a bedtime dose of an H_2RA to a PPI is not routinely recommended for adult or pediatric patients.

Monitoring Parameters

Patients receiving acid suppression therapy should be monitored for symptom relief, adverse drug reactions, and adherence to the regimen. For the management of chronic heartburn, lifestyle changes and PPIs are recommended for 12 weeks. Patients should be continually monitored during this time to determine whether therapy is providing symptom resolution. If symptoms persist at the end of the treatment period, further diagnostic testing and/or continued maintenance therapy may be required. Patients receiving treatment for reflux esophagitis should be monitored for symptom relief and the presence of any complicating symptoms (dysphagia, odynophagia). In addition, because the long term safety of all medications used for the management of pediatric GERD is unknown, careful and continued monitoring is required throughout the duration of therapy.

Symptoms associated with GERD can have a negative impact on the quality of life of both patients and their caregivers. At present, validated tools to measure the quality of life for children with GERD are limited. Practitioners most often rely on parental reports of symptoms. Assessing improvement in quality of life is important for monitoring the efficacy of treatment strategies.

Special Populations

Asthma

Reflux is known to exacerbate asthma. Gastric contents from the stomach can be aspirated into the lower airways and produce both airway inflammation and bronchoconstriction (Reference 1). From 50% to 60% of patients with asthma have abnormal pH studies (Reference 68). Nighttime cough and wheezing have been correlated with GERD. Studies have also shown that the incidence of asthma is higher in children with GER (Reference 69).

Antireflux therapy may be beneficial in patients with concurrent asthma and GER. Current recommendations for patients with persistent asthma and heartburn symptoms or regurgitation include treatment with a PPI. In addition, patients with nocturnal asthma symptoms or steroid-dependent, difficult-to-control asthma may benefit from PPI therapy once other causes of wheezing have been excluded. Therapy should be continued for 12 weeks. Antireflux surgery may also be a treatment option in the patients still symptomatic despite aggressive twice-daily PPIs and patients' adherence to their asthma medications.

Neurologic Impairment

The frequency and severity of GERD in patients with neurologic impairment are increased. It is estimated that 50% to 70% of children with neurologic impairment such as cerebral palsy have symptoms associated with reflux, and that up to 70% have endoscopic evidence of esophagitis (Reference 70). It is more difficult to properly provide a diagnosis for a child with GERD who has neurologic impairment because such children have difficulty communicating their symptoms and may present with atypical symptoms (self-injurious behavior, seizures, and dystonia). The most reliable diagnostic tool for GERD in children with neurologic impairment is pH/multiple intraluminal impedance monitoring (Reference 1). Treatment of GERD in these patients should be individualized and consist of feeding changes, positional changes, muscle spasm control, and antireflux therapy. These patients may benefit from the combination of a PPI and baclofen. Careful monitoring of baclofen's adverse effects is warranted. Baclofen can cause dizziness, drowsiness, and fatigue, as well as lower the seizure threshold. Some patients with neurologic impairment improve with medication therapy alone. Antireflux surgery should be considered in patients who do not respond to aggressive medical management and have concomitant respiratory complications. The risks and benefits must be weighed carefully because surgery in these patients has resulted in higher morbidity, mortality, and symptom recurrence.

Conclusions

Appropriate management of GER and GERD in the pediatric patient is important because symptoms can have a considerable effect on quality of life and may persist into adulthood, causing complications. The recent clinical practice guidelines provide updated information and evidence to help guide the medical management of children with GER and GERD. Many questions remain for these patients because of the lack of large, well-designed clinical trials of different age groups within the pediatric population. Pharmacists should be familiar with current guidelines so that they can provide evidence-based treatment recommendations.

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CHAPTER 17

Diarrhea and Constipation

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Learning Objectives

1. Recognize the worldwide impact of diarrhea as the leading cause of morbidity and mortality among children.
2. Explain general mechanisms of diarrhea and associated common causes.
3. Recommend appropriate management of diarrhea including both nonpharmacologic and pharmacologic therapy.
4. Identify etiologies, with constipation as a primary symptom.
5. Identify medications associated with constipation and the importance of prevention.
6. Recommend nonpharmacologic and pharmacologic treatment options for pediatric patients with constipation (both acute and maintenance therapy).

Abbreviations in This Chapter

BM	Bowel movement
GI	Gastrointestinal
ORT	Oral rehydration therapy

Introduction

Gastrointestinal (GI) disorders in children are a common cause of discomfort, family stress, and provider and hospital visits each year. Gastrointestinal disturbances can begin in the first days of life and can be a clinical indicator of an underlying physiologic or metabolic disorder, or even an infectious process. Diarrhea and constipation are two broad categories that encompass many disease or functional processes often encountered in the pediatric patient. This chapter seeks not only to outline the impact of diarrhea and constipation on children and their families, but also to provide insight into the diagnosis, treatment, and prevention of these disorders.

Diarrhea

Epidemiology

Worldwide, diarrhea continues to be a leading cause of morbidity and mortality among children. In developing countries, reported mortality rates are just less than 1.5 million for children younger than 5 years (Reference 1). For that same age group, the World Health Organization (WHO) reported a mortality rate of 14% caused by diarrhea in 2008—a percentage similar to that with pneumonia (Reference 2). However, these percentages differ greatly in developed versus developing countries. Developing countries struggle with the ability to provide safe drinking water, hygiene, and overall health and nutrition, resulting in an environment ideal for the spread of diarrhea-causing pathogens. Although overall living conditions are more favorable in developed countries, the impact of diarrhea on children should not be underestimated. Diarrhea can result from infectious and noninfectious causes, both of which contribute to the cost and significant number of hospitalizations associated with this condition (Reference 3). This chapter will focus on the noninfectious causes of diarrhea and their respective treatment. For diarrhea related to infectious etiologies, see the Infectious Diarrhea chapter.

Etiology

Diarrhea is characterized by three or more watery, loose stools per day (or more than normal for an individual). Although a precise definition has not been well described, an increased number and changed consistency of stools for less than 1 week is considered acute diarrhea. Most diarrheas occurring in children, especially those between 6 months and 2 years of age, result from an acute, infectious etiology. Although viral pathogens are the most common, bacterial and parasitic pathogens can also be implicated in diarrhea (see Infectious Diarrhea chapter). Chronic diarrhea is diarrhea lasting more than 14 consecutive days and is usually associated with chronic medical conditions or GI pathology in the pediatric population. Malabsorption syndromes, including cystic fibrosis and celiac disease, often initially present with diarrhea symptoms and should be considered when determining the etiology of new-onset, prolonged diarrhea. Celiac disease is an autoimmune condition triggered by gluten intake that damages the small intestine, preventing good absorption. Iatrogenic malabsorption secondary to short bowel syndrome is also a significant cause of chronic diarrhea. Short bowel syndrome is the result of surgical removal of portions of the intestines secondary to intestinal ischemia caused by various factors. Irritable bowel syndrome is an example of a functional bowel disorder that can cause diarrhea (see Irritable Bowel Syndrome chapter).

Nutrition may also play a role in the infant and child with diarrhea, specifically with respect to type of formula used and preparation technique. Hyperosmolar or concentrated formulas can cause fluid shifts, resulting in osmotic diarrhea. Enzyme deficiencies or food sensitivities like lactase deficiency, or the more common lactose intolerance, make it difficult to digest lactose-containing foods (e.g., milk-containing products), leading to diarrhea. Similarly, food allergies can elicit a diarrheal response when exposure occurs. Often, infants with a cow's milk protein allergy will present to the provider's office with complaints of diarrhea in addition to other allergic symptoms. Ingestion of irritating foods such as nondigestible fibers or insoluble sugar alcohols can also precipitate acute diarrhea. Another well-described etiology in children is medication-induced diarrhea. Antibiotic-associated diarrhea does not generally result in severe sequelae and resolves within a few days after the antibiotic course is completed. Recognizing the potential causes of diarrhea, both acute and chronic, can assist in the appropriate management and prevention of morbidity and mortality in the pediatric population.

Pathophysiology

Diarrhea results when the normal functions of the GI tract for maintaining fluid and electrolyte balance are impaired. The water content of fecal material determines whether stools are too liquid or too dry, which in turn affects bowel function/status. The amount of fluid in stool depends on the amount ingested through diet, the contribution from intestinal secretions in the small intestine, and the amount reabsorbed by the colon. Chyme, a semifluid mass of partly digested food and digestive secretions formed during digestion, makes up the remainder of stool content, with the absorption of partly digested fats, carbohydrates, and protein occurring as it passes into the ileum. As stool enters the colon, a large amount of water is absorbed, further changing the composition and electrolyte content of the remaining chyme/stool. Normal fecal stool has electrolyte concentrations of sodium 40 mEq/L, chloride 15 mEq/L, potassium 90 mEq/L, and sodium bicarbonate 30 mEq/L (References 4, 5). Alterations in absorption and secretion of water and electrolytes when GI function is impaired can change these values. There are four general mechanisms for disruption of water and electrolyte balance and thus four classifications, or types, of diarrhea: secretory, osmotic, exudative, and altered motility (References 4, 5).

Secretory Diarrhea

Secretory diarrhea occurs in response to some stimulating substance increasing the secretion of water into or decreasing the absorption of water and electrolytes from the intestinal lumen. Causes of secretory diarrhea include unabsorbed dietary fat, laxatives, secretin or other hormones (including those released by tumors), bacterial toxins, or increased bile salts. These agents interrupt the normal cell transport processes by stimulating intracellular cAMP (cyclic adenosine monophosphate) and inhibiting Na^+/K^+-ATPase (sodium/potassium/adenosine triphosphatase), causing the secretion of a large amount of water and indirectly preventing ion (electrolyte) absorption (References 4, 6). Although the source of these factors differs, the normal function of the intestine is ultimately compromised, resulting in an amount of water being secreted into the intestine greater than that absorbed. Clinically, this type of diarrhea is identified by large stool volumes with normal electrolyte content.

Osmotic Diarrhea

Water reabsorption in the intestine is a passive process and is dependent on the absorption of other substances. When poorly absorbed substances remain in the lumen, an osmotic gradient is created, resulting in water being pulled into the lumen producing watery, osmotic diarrhea. This type of diarrhea differs from secretory diarrhea because there is no excess secretion of a substance causing changes in the amount; rather, the mechanism for absorption is somehow impaired (Reference 6). Malabsorption, lactose intolerance, and medications including magnesium (and other divalent ions) and lactulose are associated with osmotic diarrhea. *Malabsorption*, a collective term, occurs when absorption is decreased because of the inability to digest or absorb a particular nutrient. Altered motility or altered digestion (e.g., pancreatic insufficiency), as previously described, contributes to malabsorption. Decreased absorption of solutes and fluid can also result when intestinal cells are damaged by bacterial/viral infection. Determining the cause of malabsorption can assist with treatment decisions. For example, when osmotic diarrhea is dependent on ingested substances, fasting will decrease or eliminate symptoms.

Exudative Diarrhea

When injury occurs to the mucosal lining of the intestinal tract, exudative diarrhea can occur. Injury can result from inflammation or ulceration, leading to a loss of mucus, serum proteins, or blood into the lumen. The damaged, or inflamed, intestine prevents water and electrolytes from being absorbed, leading to diarrhea. Inflammatory bowel diseases such as Crohn disease and ulcerative colitis are associated with this type of diarrhea. The presence of a large amount of exudates (mucus, proteins, and/or blood) in the stool is characteristic in patients with these inflammatory bowel diseases. Invasive infectious diarrhea can also present with similar

symptoms and, on initial presentation, is often indistinguishable from inflammatory bowel disease (References 4, 6).

Altered Motility

Diarrhea caused by altered motility is multifactorial and can involve several mechanisms, including reduction in small intestine contact time, bacterial overgrowth, and/or early emptying of the colon. Decreased exposure of material to the small intestine leads to reduced time for the normal absorption and secretion processes to occur, thus changing the composition of intestinal contents. The resulting changes in osmolarity can lead to diarrhea. Surgical resection of the gut (as in short bowel syndrome) and a medication like erythromycin or metoclopramide cause a decrease in exposure time to the small intestine. Conversely, if transit time is increased (slowing), bacterial overgrowth may occur, precipitating diarrhea. Diarrhea caused by altered motility is usually associated with sporadic and fast peristaltic waves that impair the absorption of water and prematurely move material into the colon.

Clinical Presentation and Diagnosis

Diarrhea is regarded as either acute or chronic and is differentiated by duration of symptoms. Signs and symptoms can vary depending on the underlying cause, and may be helpful in the diagnostic process. For example, acute diarrheal symptoms secondary to viral gastroenteritis include abrupt onset of nausea, vomiting, abdominal pain, headache, and fever lasting for 10–60 hours (see the Infectious Diarrhea chapter for more detail). Chronic diarrhea is more difficult to diagnose because of varying "normal" bowel patterns. In general, clinical symptoms of diarrhea include an increase in the frequency of stool, an increased stool volume, and a decrease in stool consistency. Because the differential diagnosis for diarrhea is lengthy (Table 1), qualifying the frequency, onset, consistency, and proposed mechanism is necessary when evaluating patients who present with diarrhea. A thorough patient history should also be completed and should include medication and supplement history, recent travel, drinking water type, and diet (e.g., consumption of raw meats; increased intake of fruits, fruit juices, sugar-free food).

Table 1. Common Causes of Diarrhea

Causes	Examples
Infectious	• Viral Cytomegalovirus, adenovirus, rotavirus, norovirus • Bacterial *Salmonella*, *Yersinia, Escherichia coli, Shigella, Campylobacter, Clostridium difficile* • Parasitic *Giardia*, *Entameba histolytica, Cryptosporidium, Microsporidia*
Toxins	• *C. difficile* toxin • Enterotoxins (from enteric organisms)
Exposures	• Radiation enteritis • Chemotherapy • Laxative abuse • Medications (e.g., antibiotics, magnesium-containing antacids) • Tumor-associated increased secretion
Malabsorption	• Pancreatic insufficiency • Celiac disease • Chronic liver disease • Allergic enteropathy • Glucose galactose transport defect
Inflammatory bowel disease	• Ulcerative colitis • Crohn disease • Eosinophilic gastroenteritis • Allergic colitis
Genetic-metabolic disorders	• Malabsorption syndromes
Chronic nonspecific diarrhea/ toddler diarrhea	• Usually exacerbated by a low-fat, high-carbohydrate diet in infants to toddler age
Overfeeding	• Large quantity of carbohydrate-rich foods in infancy combined with decreased amylase concentration

Clinical and Diagnostic Evaluation Criteria

Evaluation of stool characteristics can be helpful in determining the etiology of diarrhea. Frequency, consistency, volume, and even color of stool should be evaluated in a patient with diarrhea. A large amount of watery, foul-smelling stool containing undigested food suggests diarrhea originating from the small intestine, whereas diarrhea with red blood present suggests the colon as the origin. The physical examination is important in evaluating disease severity as well as hydration status. Often, the examination will lead to a more focused evaluation and aid in treatment approach. Pertinent findings on physical examination include abdominal tenderness and/or cramping as well as bloating. Vital signs including blood pressure, temperature, and heart rate should be evaluated. The presence of a fever may indicate an infectious etiology, whereas a decreased blood pressure could signify impending shock secondary to dehydration from diarrhea. Assessment of hydration status is an extremely important part of the evaluation in pediatric patients with diarrhea. Diarrhea can quickly lead to dehydration. In addition to vital signs, hydration status can be assessed by examining urine output (or number of wet diapers per day in infants), mucous membranes, tear production, and physical and mental status changes. A dehydrated patient would have decreased urine output or fewer wet diapers, dry mucous membranes or crying without tears, a sunken appearance around the eyes or cheeks, decreased skin turgor, weight loss, and mental status changes. Dehydration severity is discussed in detail in the Fluids and Electrolytes chapter.

Stool studies are generally not required unless the diarrhea persists beyond 24 hours or unless a specific diagnosis (e.g., malabsorption or confirmation of an infectious etiology) is needed. Symptoms including bloody stools and fever, systemic illness, severe dehydration, recent antibiotic use, or need for hospitalization all warrant stool testing. Several studies are available to assist with diagnosis. The presence of fecal leukocytes indicates an inflammatory response, either infectious or inflammatory bowel disease in origin. If positive, a stool culture may be warranted. The stool cultures and testing are completed if an infectious cause is suspected because of clinical findings and patient history. Rotavirus, for example, can be diagnosed within the same day as stool sample collection through specific kits or antibody serologic testing. Antibody serologic tests, however, are not specific and, as with rotavirus, can be time-dependent for accurate results. Together with cultures, the stool can be evaluated for the presence of ova and parasites. Testing for *Clostridium difficile* in patients with diarrhea with recent use of antibiotics or hospital-acquired diarrhea is completed by a rapid ELISA (enzyme-linked immunoassay). A stool analysis can also be evaluated for the presence of mucus, fat, osmolarity, pH, and electrolyte content (Reference 4). Radiographic studies, endoscopy, or a biopsy may be warranted in severe or difficult diagnostic cases, including those in which inflammatory disorders or cancer may be suspected.

Course and Prognosis

The underlying etiology of diarrhea is a key indicator of the duration of symptoms and clinical manifestations. Most acute cases of diarrhea are self-limiting. Acute diarrhea secondary to infectious cases may require antibiotics (see the Infectious Diarrhea chapter). Diarrhea associated with chronic medical conditions (e.g., Crohn's disease) may not be completely resolved, and only temporary symptomatic relief is achieved without treating the primary cause. Although diarrhea itself is uncomfortable, the complications of it, from severe or prolonged diarrhea, can be life threatening. Dehydration is the most common complication of diarrhea and should be managed carefully, especially in children younger than 2 years. This population is at particular risk because water constitutes a larger portion of their body composition compared with adults, together with a decreased ability for their kidneys to conserve water. In severe cases, electrolyte and fluid imbalance may lead to additional morbidities that require immediate attention, including seizures or hypovolemic shock. Malabsorption and related conditions are often linked to chronic diarrhea and should be managed accordingly. This generally involves supplementation of any electrolyte or nutrient deficiency as well as some mechanism for slowing transit time. Many times, the exact etiology of acute diarrhea is not known, but a thorough evaluation and differentiation of potential causes are important to provide adequate treatment and predict the clinical course.

Noninfectious Diarrhea

Antibiotic Therapy

Antibiotic therapy is associated with diarrhea in about 60% of all children prescribed antibiotics (Reference 5). Proposed mechanisms for antibiotic-associated diarrhea include alteration of gut flora leading to decreased carbohydrate transport and increased intestinal lactate levels. Decreased carbohydrate transport from the gut leads to increased osmolarity and increased secretion of water into the stool. Diarrhea associated with antibiotic use is described as watery, but it should not have any systemic symptoms. Once the antibiotics are discontinued, the diarrhea should resolve (Reference 7). Another consequence of antibiotic therapy that may result in diarrhea is a *C. difficile* infection. *C. difficile* is part of the normal GI flora, but when antibiotic therapy alters the normally balanced flora, the bacteria can become

pathogenic. The toxins produced by *C. difficile*, which occurs in up to 10% of patients taking antibiotics, can lead to pseudomembranous colitis (see Infectious Diarrhea chapter) (References 8–11).

Malnutrition

Nutrition and diarrhea have a bidirectional relationship. Malnutrition's role in chronic diarrhea stems from the increased risk of enteral infections and relationship to malabsorptive syndromes. A lack of nutrition leads to increased infection risk because of the effect on host immune function and alterations in the protective barrier of the gut mucosa. Diarrhea can also precipitate malnutrition by decreasing the absorption of nutrients, further worsening the overall clinical effects of both (Reference 12). However, the cause of malnutrition may be multifactorial and include frequent infections, bile acid malabsorption, decreased pancreatic enzyme activity, altered motility, decreased intestinal surface area, and changes in intestinal flora. Treatment considerations for malnourished patients with diarrhea should be comprehensive and address both disease states.

Diet

Infant nutrition can be a major player in diarrhea, caused by overfeeding or general developmental differences. Overfeeding, particularly in the first few weeks of life and with a high-calorie formula, can lead to diarrhea. Developmentally, neonates have a deficiency in the pancreatic enzyme amylase, thus increasing the carbohydrate content in the stool, causing diarrhea (Reference 5). Amylase is the enzyme responsible for the breakdown of carbohydrates, and as amylase function develops, increased carbohydrate load can be handled. Drinks or foods containing a large amount of sorbitol or fructose may also cause an osmotic diarrhea. Foods that are spicy, that are difficult to break down (insoluble fibers like raw vegetables and nuts), or that contain or release histamine (e.g., tomatoes, cheeses, citrus fruits, fish) may also contribute to diarrhea (Reference 5). Additionally, lactose intolerance, the inability to digest and/or metabolize lactose, may contribute to diarrhea. Lactose is a sugar found in milk and milk products, and generally, intolerance is caused by a deficiency in the enzyme lactase. Lactase is produced by the cells lining the small intestine, which breaks down lactose into the absorbable sugars glucose and galactose. Children younger than 2 years generally do not have diarrhea related to lactase deficiency because this is the period of highest production. In older children and adults, lactase production decreases, causing an increase in the incidence of lactose intolerance. The exact incidence and age of onset for lactose intolerance varies among different ethnic groups, with those having diets high in dairy products experiencing a lower occurrence (Reference 13). This can be treated by avoiding high lactose–containing foods and taking over-the-counter lactase enzyme–containing medications. Temporary milk intolerance after an acute viral gastroenteritis can also occur. With acute gastroenteritis, the absorptive lining, which also produces lactase, is damaged, causing a transient enzyme deficiency and resulting intolerance. Short-term use of lactose-free formulas can be used in infants, but any formula changes should be discussed with the provider before changing the diet. Avoidance of high lactose–containing foods and slow reintroduction can be implemented as antibiotic therapy is discontinued (Reference 13).

Diarrhea can occur in infants younger than 6 months who are exposed to cow's milk or infant feeding formula. Breastfed infants usually have a softer stool than those receiving cow's milk, but if acute diarrheal symptoms are present in breastfed infants, infectious causes should be considered until another diagnosis is made versus discontinuing breastfeeding. Formula feeding, which is generally associated with firmer stools, may lead to diarrhea, especially with the use of high-calorie formulas or those high in sugar content. To avoid changing formulas frequently or discontinuing breastfeeding, providers will perform a thorough history to determine the cause of acute diarrhea before altering the infant's nutrition.

Allergic Diarrhea

Diarrhea caused by an allergy to milk proteins is most common in infants younger than 1 year and can be resolved by switching to a soy or elemental formula. The overall incidence of milk protein allergy in infants is between 0.5% and 1% (Reference 5). Milk allergies typically resolve by 12 months, and patients can be rechallenged at that time. Of interest, a family history of atopy may increase the risk of having a protein allergy (Reference 5). Breastfeeding mothers should avoid dairy products if a milk protein allergy is confirmed. Flecks of blood in the stool of an otherwise healthy infant may be a defining symptom of milk protein intolerance. Slow introduction of dairy products into the diet and observation of diarrhea symptoms should be noted. If the sensitivity continues in older children (e.g., school-aged children and older), a protein allergy, presenting as a celiac-like disorder, may be considered. Allergies to other foods may be diagnosed by challenging the patient with the suspected offending food under close supervision. Immunoglobulin E–mediated food allergies, other than milk, generally last a lifetime and will not be outgrown, including peanut, egg, and fish allergies. Allergic responses will often include an anaphylactic-type reaction, including vomiting, diarrhea, hypotension, and pallor (Reference 5). Recently, increased awareness of gluten allergy led to increased availability of gluten-free

products. Gluten is a protein contained in wheat, rye, and barley and is implicated in intestinal damage in the autoimmune disorder known as celiac disease. It is recommended that patients with celiac disease avoid gluten-containing foods.

Chronic Nonspecific Diarrhea

In healthy children, chronic nonspecific diarrhea, also known as "toddler diarrhea," is a common reason for loose stools. A flu-like illness or recent use of antibiotics will usually precipitate symptoms. Occurring most commonly in children between 9 months and 3½ years of age, the otherwise healthy and thriving toddler may have six to eight "runny" stools per day. Usually by the time the child reaches 3½ years, no other diagnosis is made regarding the etiology, and symptoms subside (Reference 5). Although no definitive cause has been established, several associations have been reported. Low-fat, high-carbohydrate diets tend to make stools increasingly loose, which can worsen during stress or illness. Toddlers drinking a large amount of high-sugar fruit juices, parents or caregivers overfeeding or underfeeding the child, and the child's ingestion of irritating foods (including tomatoes and citrus) are other associations. This type of diarrhea is symptomatically similar to irritable bowel syndrome in adults (Reference 5). Trying a high-fat, low-carbohydrate diet, as well as minimizing the amount of high-sugar drinks, helps relieve symptoms.

Treatment

Although prevention of acute diarrhea secondary to infectious causes plays the biggest role in worldwide efforts to decrease mortality and morbidity, prompt treatment of diarrhea is equally important. The goals of therapy first include prevention and management of water and electrolyte imbalances to restore normal hydration status. Other goals include providing symptomatic relief, treating the underlying cause, and managing the diet or other secondary causes of diarrhea.

Nonpharmacologic Therapy

The two main components of nonpharmacologic management of diarrhea are restoring fluid and electrolyte balance and making temporary dietary modifications during the acute illness. Fasting is generally not necessary if the patient can tolerate eating—though type or amount of food ingested may need to be modified (i.e., avoid excessively fatty, spicy, or processed foods or those known to upset the stomach). Guidelines generally recommend early introduction of appropriate food and liquids during the replacement process, if patients can tolerate it (Reference 14). It is currently recommended that for acute diarrhea, feeding should continue, except in a formula-fed infant with severe diarrhea during the initial rehydration period. It is not necessary to initiate only clear liquids or the BRAT (bananas, rice, applesauce, and toast) diet, which may, in fact, prolong diarrhea. This "starvation" method may prevent cellular repair and generation. A low-residue diet, or one that is easily digestible, is recommended when vomiting and diarrhea are present, unless vomiting is severe enough that nothing should be taken by mouth. Emphasis has been placed on the continuation of feeding during an acute episode of diarrhea, which is a shift in thought from restricting food because it may cause or worsen diarrhea (i.e., the ingested food is causing the diarrhea). Because most diarrhea cases are self-limiting and dehydration remains a significant risk in this age group, the benefits of feeding outweigh any risk. Treatment recommendations maintain that for breastfeeding infants with diarrhea or children with infectious acute diarrhea, feeding should continue, which has been shown to decrease morbidity and mortality (Reference 4). Older children can resume "normal" fluids and solids, but they should avoid fatty foods or those high in simple sugars (Reference 14). Maintaining nutrition also plays an important role in the management of chronic diarrhea. Proper caloric intake is important for all age groups and etiologies because feeding will assist in intestinal repair.

Water and electrolyte replacement is the cornerstone in the management of dehydration associated with diarrhea. Fluid replacement can be with oral or intravenous therapy, depending on the patient's severity/level of dehydration. Determining the severity of dehydration and evaluating the progress of maintaining hydration are particularly important in children younger than 2 years. The combination of risk factors, including being more susceptible to dehydration because of a lack of reserve and the difficulty of determining the effectiveness of rehydration techniques, necessitates close observation and a low threshold for seeking advanced care. Careful clinical observation for signs and symptoms of dehydration and obtaining a good patient history can aid in selecting the best individualized pathway for treatment.

Severe dehydration is characterized by dry mucous membranes, loss of skin turgor, delayed capillary refill, tachycardia, and even signs of shock. Mild and moderate dehydration involves dry mucous membranes, increased thirst, sunken eyes and fontanelle, and some loss of skin turgor. Further discussion of mild, moderate, and severe dehydration is included in the Fluids and Electrolytes chapter. For mild and/or moderate dehydration, oral rehydration therapy (ORT) is preferred and is as effective as intravenous therapy in these patients (Reference 14). Patients with severe dehydration, sepsis/shock, or systemic complications need intravenous fluid resuscitation. Fluid management includes both a rehydration

and maintenance phase. In the first few hours, the goal of rehydration therapy is to rapidly restore water and electrolytes to normal concentrations. After rehydration has occurred, maintenance therapy is given to replace ongoing losses (i.e., maintain normal body composition) and provide therapy until dietary intake can be initiated (see Fluids and Electrolytes chapter). It is important to remember that the reintroduction of feeds, either breastfeeding or formula, is encouraged and supported for infants as a means of maintaining proper fluid balance.

Several commercially available ORT products are available—some are premixed solutions, and others are dry powder packets to which water must be added. The solution, consisting of glucose and salts in specific ratios to aid in intestinal absorption, is absorbed in the small intestine as a replacement for what is lost in the stool. These products vary in the amount of glucose, sodium, and other electrolytes they contain (Table 2). Products with a sodium content of 75–90 mEq/L are intended for use as rehydration solutions, whereas the sodium content of maintenance solutions is between 40 mEq/L and 60 mEq/L (References 7, 14). The rationale for the composition of these products is based on the glucose-sodium cotransport system in the GI tract. In this system, the linkage of glucose and sodium molecules allows glucose to carry sodium into the cells of the small intestine. Water then follows sodium into the bloodstream, resulting in increased absorption of both water and sodium (Reference 15). The ORT products also contain potassium and chloride to replace losses, and citrate, which converts to bicarbonate, is added to correct the acidosis associated with dehydration. For these reasons, ORT products are superior to the "clear-liquid" diets often prescribed to patients with diarrhea. Because the composition of many household "clear liquids" is not formulated specifically for rehydration, the concentrations of electrolytes and glucose-to-sodium ratio are inappropriate, and the amount of sugar is often too high for adequate replacement of stool losses.

Specifically in developing countries where educational levels and languages may vary, the WHO and UNICEF (United Nations Children's Fund) recommend using a single oral rehydration solution (the WHO ORS) to avoid mixing errors that would result in the administration of a solution with the incorrect concentration. The high salt content of some ORT products has raised concerns about the use of the higher-sodium solutions in well-nourished children with less severe dehydration who may not need the same level of salt replacement because it may cause hypernatremia. However, studies have shown the ORS to be quicker in the correction of dehydration and safer than intravenous fluids (References 14–18). Some available ORT products are rice-based oral solutions, which provide glucose for the cotransport system from the breakdown of complex carbohydrates in rice/cereal without increasing the osmotic gradient, as can occur with glucose-based products. Overall, oral rehydration remains safe and effective when using the approved ORT products. Fluids for rehydration in developed countries should also be carefully considered. Many fruit juices are high in sugar content and have a high osmolality with no electrolytes. Higher sugar content and osmolality solutions can cause an osmotic diarrhea, worsening dehydration status. Solutions with no electrolytes will not replace what is lost and can lead to detrimental effects related to the lower serum concentrations of these electrolytes. Examples include hypokalemia causing muscle weakness as well as hyponatremia resulting in seizures. Lower osmolar fluids that are more like the ORT products are preferred. Examples of these fluids are listed in

Table 2. Commonly Used Oral Rehydration Fluids and Composition

Solution	Osmolality (mOsm/L)	Glucose (g/L)	Sodium (mEq/L)	Bicarbonate (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Pedialyte (Ross Laboratories)	250	25	45	30	20	35
Enfalyte (Mead-Johnson)	200	30	50	34	25	45
Rehydralyte (Ross Laboratories)	305	25	75	30	20	65
WHO ORS	245	13.5	75	30	20	65
CeraLyte (CERA Products)	220	40	50–90	30	20	—

ORS = oral rehydration solution; WHO = World Health Organization.

Table 2. Overall, water, carbonated sports drinks, caffeinated drinks, and sweetened tea are not acceptable for rehydration because these beverages do not provide adequate electrolytes for replacement or because they are hyperosmolar (References 14, 15).

Pharmacologic Therapy

Outlining the use of pharmacologic therapy as treatment for diarrhea in the pediatric population has been difficult because medications and other pharmacologic agents are used solely for supportive care in the management of diarrhea (Table 3). Different classes of medications and supplements have been used to alleviate symptoms including opiates and their derivatives, cholestyramine, psyllium (adsorbents), probiotics, bismuth subsalicylate, zinc, and vitamin A. Although each of these has been shown to provide some benefit in alleviating symptoms, guidelines are still lacking for their use in the infant and toddler population. Choosing an agent should include balancing efficacy and safety. Knowing the ways that such medications work and the related adverse effects can assist in making the proper recommendations.

Opioids, by acting on the mu receptors in the GI tract, delay GI transit time and prolong contact time. Action on these receptors also leads to the well-known adverse effect of constipation (and can lead to ileus) associated with this class. The opioids tincture of opium, paregoric (morphine 2 mg/5 mL), and diphenoxylate have been studied in the treatment of both acute and chronic diarrhea. Because of drug abuse potential and the risk of ileus, these medications are not widely prescribed for symptomatic treatment of diarrhea. Diphenoxylate is an opioid derivative available in combination with atropine that is used in noninfectious diarrhea, particularly for chronic diarrhea. Atropine is added to the formulation to prevent abuse by causing undesirable anticholinergic effects. Children with malabsorption secondary to short bowel syndrome may benefit from combination therapy of diphenoxylate/atropine and loperamide.

Loperamide, an opioid derivative, does not cross the blood-brain barrier like other opioids and is thus void of the associated analgesic and central nervous system effects of other opioids. Loperamide acts like other opioids by delaying GI transit time and acts peripherally as an antisecretory agent, regulating chloride secretion. Because water will follow chloride ions, a decrease in water would likely help reduce diarrhea. However, its place in the therapy of acute diarrhea is limited. A recent meta-analysis of loperamide in pediatric patients found that children younger than 3 years who are malnourished, are severely dehydrated, or have bloody diarrhea are at increased risk of adverse events from loperamide, including lethargy, abdominal distention, and ileus. In addition, cases of necrotizing enterocolitis have been reported with loperamide use in children younger

Table 3. Pediatric Dosing for Select Antidiarrheal Agents

Loperamide	**Acute Diarrhea:** 2–5 years (13–20 kg): 1 mg three times/day 6–8 years (21–30 kg): 2 mg twice daily 9–12 years (> 30 kg): 2 mg three times/day After initial dosing, 0.1 mg/kg after each loose stool, but not to exceed initial daily dosing[a] **Chronic Diarrhea:** 0.08–0.24 mg/kg/day divided two or three times/day, maximum 2 mg/dose
Paregoric	0.25–0.5 mL/kg one to four times/day
Diphenoxylate and atropine	**Initial:** 0.3–0.4 mg/kg/day (max 10 mg/day) in four divided doses or manufacturer's recommended dosing: < 2 years: not recommended 2 years (11–14 kg): 1.5–3 mL four times/day 3 years (12–16 kg): 2–3 mL four times/day 4 years (14–20 kg): 2–4 mL four times/day 5 years (16–23 kg): 2.5–4.5 mL four times/day 6–8 years (17–32 kg): 2.5–5 mL four times/day 9–12 years (23–55 kg): 3.5–5 mL four times/day **Maintenance:** Can give 25% of initial dose
Cholestyramine	240 mg/kg/day in three divided doses; titrate on the basis of indication

[a]Taken from Takemoto CK, Hodding JH, Kraus DM. Pediatric & Neonatal Dosage Handbook, 18th ed. Hudson, OH: Lexi-Comp, 2011 (Reference 19).

than 2 years. Therefore, loperamide should not be used routinely in this population. However, loperamide has been used in this younger population if the patient has short bowel syndrome to help with malabsorption (References 20, 21). Loperamide should not be used in most infectious diarrhea cases because impairing/slowing GI transit in patients with infectious diarrhea caused by a toxin-producing bacteria carries the risk of preventing toxins from being cleared from the GI tract. This is especially important in these cases because the toxins are largely responsible for the intestinal damage that occurs. Loperamide may have a use in chronic diarrhea, especially in patients with malabsorption problems.

Cholestyramine, a chloride and basic quaternary ammonium anion exchange binding resin, has been used in diarrheal disorders involving increased fecal bile acids or pseudomembranous colitis. Cholestyramine forms a nonabsorbable complex with bile acids in the intestines and causes the release its chloride ions during this process. The chloride ions are absorbed, allowing water to follow, thus decreasing diarrhea. Pediatric patients may be at increased risk of hyperchloremic acidosis as a result; however, studies evaluating the role of cholestyramine in children 7 months to about 2 years of age with acute and chronic diarrhea have shown that shortened courses (by about 2 days) are tolerated without significant adverse effects (Reference 17) after adequate hydration with ORT. When administering cholestyramine with other medications or supplements, medications should be given at least 1 hour before or at least 4–6 hours after cholestyramine to prevent binding and decreased absorption of other medications and with plenty of water to prevent constipation (Reference 19).

Psyllium or other adsorbents are used for symptomatic relief and are nonspecific in their action. As bulking agents, these drugs absorb liquid in the GI tract, which alters the fluid and electrolyte content and expands the stool (forms "bulk"). These agents can also absorb digestive juices, nutrients, or medications, which may reduce their bioavailability. Although psyllium can be used as a laxative, its bulk-producing properties may help create a more formed stool and can be beneficial in patients with diarrhea. Psyllium can prevent the absorption of medications, so other medications should not be taken within 3 hours of psyllium administration. Psyllium should also be taken with plenty of water because it is a bulking agent and can cause constipation, leading to obstruction (Reference 19).

The use of probiotics for diarrhea in children has recently gained momentum with the introduction of many lactobacillus products and dosage forms. Other bacterial probiotics studied in this population include *Bifidobacterium lactis* and *Streptococcus thermophilus. Saccharomyces boulardii* is a non-pathogenic yeast that was recently studied for its use in the treatment of diarrhea; however, few data exist in the pediatric population. Probiotics, found in normal gut flora, have been shown to decrease or prevent diarrhea associated with antibiotic use and to benefit children at risk of infectious diarrhea related to malnutrition or pathogen exposure (References 22, 23). The mechanism of probiotics in the treatment of diarrhea is not well understood. Presumed mechanisms of benefit include enhancement of the immune system, creation of a competitive environment for microbial growth, or extension of antimicrobial action on pathogenic organisms. Despite increased use, controversy exists regarding the potential risk of seeding the organism from the gut into the bloodstream (resulting in bacteremia with lactobacillus or fungemia with *Saccharomyces*), especially in neonatal or immunocompromised populations. A meta-analysis of the use of lactobacillus for acute infectious diarrhea found a reduction in the number of stools and overall safety profile (Reference 22). This analysis predominantly included children 1–36 months of age. No studies included the neonatal or premature neonatal populations. Prebiotics, food, or supplements with nondigestible substances that facilitate microbial growth of indigenous probiotic bacteria have also been introduced as a preventive or symptomatic treatment of diarrhea. More studies are needed to assess the true benefit of probiotic and prebiotic use and evaluate the potential for adverse effects in high-risk populations (Reference 23).

The use of zinc and vitamin A has also been described in the treatment of childhood diarrhea. Zinc is an essential mineral that plays a role in immune function; it has been extensively studied in pediatric patients in developing countries (References 24, 25). These patients may be zinc-deficient secondary to malnutrition, and the extrapolation of these results to use in developed countries may not be as well-founded. The exact mechanism of zinc's role in the treatment of diarrhea is not fully understood. Zinc may have a role in enhancing cation absorption or suppressing cation secretion. Several studies of children 1–60 months of age with either acute or persistent diarrhea show a reduction in stool frequency and overall incidence of diarrhea (Reference 26). However, controversy exists regarding the most appropriate dose and dosage form. Because of the potential concern for copper deficiency with long-term use of zinc, the WHO recommends only a 10- to 14-day course (of 10–20 mg/day) for treatment of acute diarrhea (Reference 16). Zinc, which is well tolerated, has not shown any significant adverse effects with short-term use. Copper deficiency leading to anemia has been described and should be evaluated if prolonged therapy is used.

Vitamin A supplementation has also been investigated in malnourished children of developing countries with mixed results. Of the children studied, those with a wasting syndrome responded best to vitamin A (Reference 27). As with zinc, those deficient in vitamin A may have better outcomes from supplementation, and routine use for the treatment of diarrhea is not currently recommended (Reference 27).

Bismuth subsalicylate has been used for traveler's diarrhea, for chronic infantile diarrhea, or as an adjunctive treatment for *Helicobacter pylori*–associated gastritis. Bismuth subsalicylate is thought to work by dual mechanisms. Bismuth acts by facilitating the absorption of extra water in the intestines as an antisecretory agent. When the subsalicylate is hydrolyzed into salicylic acid, it inhibits prostaglandins associated with inflammation and possible hypermotility. Bismuth subsalicylate may even have antimicrobial effects by binding toxins or because of some inherent bactericidal activity. Because all products contain salicylates, caution should be used in individuals with chickenpox or influenza, secondary to the risk of Reye syndrome.

Overall, treatment of diarrhea in the pediatric population consists of careful monitoring, prevention of dehydration, and provision of symptomatic care when appropriate. Recommending pharmacologic treatment of diarrhea should first include analyzing the etiology and age group. Medication use should be approached with caution and selected according to the clinical condition of the patient, any comorbidities, and potential for adverse effects. Hydration status remains the underlying theme of diarrhea management and thus the recommendation with the most evidence-based support. Most acute diarrhea algorithms will follow a dehydration assessment and treatment plan and suggest antidiarrheal medications only as last-line symptomatic relief. The caveat to this would be if the diarrhea were infectious in origin. Separate treatment algorithms exist for infectious diarrhea as described in the Infectious Diarrhea chapter.

Monitoring of Therapy

The most important monitoring parameter with diarrhea is hydration status. Determining the degree of dehydration initially and evaluating for improvement in hydration status will help direct therapy changes in rehydration fluids. Once initial deficits are accounted for and maintenance therapy is initiated, the decision to reinitiate feeds or trial of oral nutrition should be considered. Symptoms of acute diarrhea should subside within 24–72 hours. Decreased number of and more formed stools, together with decreased clinical symptoms of pain and bloating, indicate improvement and response to therapy. Daily examination of body weight with fluid balance totals (input/output) should be monitored because this will help determine hydration status. Serum electrolytes may also need to be monitored to ensure the correction of any deficiencies. For infectious causes, a complete blood cell count, urine analysis, and blood or stool cultures are all appropriate monitoring parameters. Chronic diarrhea treatment should focus on treating/managing the underlying cause, together with any symptomatic relief measures. Careful monitoring of hydration status and signs of treatment response is the overriding principle of diarrhea management.

Constipation

Constipation is a common problem among children and adults and is responsible for many physician, hospital, and specialty visits each year. In 2006, an estimated 5.7 million physician visits were for constipation alone (Reference 28). Even though constipation is a common and well-known condition, many different definitions have been used to describe and diagnosis it. Health care practitioners (e.g., physicians, nurses, pharmacists), researchers/epidemiologists, and patients may all describe constipation differently, with some using frequency of bowel movements (BMs) or stool characteristics and others referring to change from their own normal pattern. Even when a general definition of constipation is used—such as "the passage of bulky or hard stool at infrequent intervals"—what is "normal" for one patient may not be the same for another, leaving much to subjective interpretation. In addition, different age groups have different stooling habits as well as exposure to different diets, making it difficult to define exactly what constitutes "normal" bowel habits in the pediatric population. For example, breastfed infants are rarely constipated and often have several BMs per day, whereas older children typically have less frequent BMs per day—though the number can vary markedly, even between children of the same age (Reference 29).

Definitions and Epidemiology

Constipation can be defined as having infrequent stools (less than 3 BMs per week), having hard stools, experiencing excessive straining, or having a feeling of incomplete evacuation. Thus, what defines constipation for each case must be individualized for the patient. Pediatric definitions, integrated into the Rome III criteria in 2006, define childhood constipation as follows:

> the occurrence of two or more of the following six criteria in the previous 8 weeks: frequency of movements fewer than 3 a week; more than one episode of faecal incontinence a week; large stools in the rectum or palpable on abdominal

examination; passing of stools so large that they may obstruct the toilet; retentive posturing and withholding behaviour; and painful defecation. (Reference 30)

Constipation can be classified as "functional constipation." This is defined as follows:

> [the] occurrence of two or more of the following six criteria in the previous 2 months in a child with a developmental age of at least 4 years, who has insufficient criteria for the diagnosis of irritable bowel syndrome (including no evidence of an inflammatory, anatomic, metabolic, or neoplastic process): two or fewer defecations in the toilet a week; at least one episode of fecal incontinence a week; history of retentive posturing or excessive volitional stool retention; history of painful or hard BMs; presence of a large faecal mass in the rectum; and a history of large-diameter stools that may obstruct the toilet. Infants up to 4 years of age have to fulfill two or more criteria for at least 1 month,

according to Rome III criteria. It is important to remember that the definition of constipation is not based on frequency alone, but also on complete evacuation of the large colon and consistency. A child who has several small stools per day and is not completely evacuating the large colon is considered constipated versus a child who has large stools twice a week but evacuates the colon.

Determining the overall incidence of constipation is difficult because it is complicated to define. The prevalence of childhood constipation, both acute and chronic, has been estimated as anywhere from 0.7% to 29.6% in the general population worldwide (Reference 29). In the United States and United Kingdom, the incidence of chronic constipation is reportedly lower at 1% to 5% (Reference 29). One-half of children with a history of painful defecation develop chronic constipation and its complications, including fecal impaction and/or fecal incontinence. Ninety percent of pediatric chronic constipation cases are a result of withholding behavior (a type of functional constipation), rather than an organic or pathologic cause (Reference 28). Still, constipation comprises 25% of pediatric visits to a gastroenterologist (Reference 29).

Certain risk factors for constipation have been evaluated. One study found a higher incidence of constipation among children with a birth weight less than 750 g and in the presence of neurodevelopmental impairments (Reference 30). A low-fiber diet may also predispose a patient to constipation (Reference 31). As the number of those with childhood obesity climbs, evidence has shown a higher prevalence of constipation and fecal incontinence among these children (Reference 32).

Pathophysiology and Etiology

Continence is maintained by muscular contractions of both the internal (involuntary) and external (voluntary) anal sphincter. When stool comes in contact with the mucosa of the lower rectum, an urge to defecate is triggered. Defecation can be controlled by tightening the external sphincter and gluteal muscles, which push the feces away from the lower rectum and eliminate the sensation to have a BM. Withholding causes the rectum to stretch (to accommodate the extra stool), resulting in a decreased ability and sensitivity to pass stool. In addition, because the fecal matter stays in the rectum, it becomes harder, making it painful to pass. This can lead to a cycle of withholding behavior and increased anxiety in the child. This description is known as functional constipation; however, constipation may also result from an organic cause. Stool patterns vary in pediatric patients, making it difficult to define what is abnormal in this population and to accurately identify the underlying cause. Therefore, each patient should be evaluated individually when diagnosing constipation.

Anatomic, dietary, and/or medication-related causes should be considered in the differential for constipation. Organic causes of constipation include neurologic (spina bifida or cerebral palsy), Hirschsprung disease, chronic intestinal pseudo-obstruction, and neuronal intestinal dysplasia. Hirschsprung disease is a condition in which the nerves (or ganglions) at the end of the colon are missing, causing the absence of peristalsis and resulting in obstruction with stool. Surgery and supportive care, including medications and maintaining an appropriate diet, are involved in the treatment of these organic causes. Cystic fibrosis and systemic lupus erythematosus have also been linked to constipation and are managed similarly with medications and diet modifications. Metabolic and endocrine disorders may also affect bowel function. Hypothyroidism, diabetes mellitus, and hypercalcemia can inhibit bowel function and should be ruled out with an appropriate workup and/or managed accordingly if present (References 31, 32).

Diet can also be a factor in causing constipation, particularly those diets low in fiber and in the presence of dehydration. In infants, breastfeeding or formula feeding is rarely associated with constipation unless there is an insufficient amount of food. Constipation in this age group should be evaluated for feeding and anatomic or neurologic etiologies. Changes in diet in older children, particularly an increase in high-fat, low-fiber diets together with decreased water consumption, can precipitate constipation.

Medications have also been implicated in causing constipation. The abuse of cathartics, or agents that induce stooling, can cause a delay in stooling and begin a cycle of daily or frequent use to maintain "normal" bowel

function. Education on the proper use of cathartics and "normal" bowel habits is an important part of constipation management. The caregiver should understand that "normal" may not include a daily BM, but as long as the colon is being emptied fully, medications are not necessary to facilitate defecation. Overuse of laxatives can cause a physical dependence and, if stopped, will result in constipation. Other medications that cause constipation, not through dependence but through effects on motility, include opioid narcotics, antihistamines, antidepressants, antacids (especially calcium-containing products), pseudoephedrine, and the chemotherapy agent vincristine, among others (Box 1). Iron supplementation, commonly used in the pediatric population with multivitamin products, may also lead to constipation. Caregivers should watch for any changes in stool habits in infants and children taking iron.

Box 1. Medications known to cause constipation.

Antidepressants/Antipsychotics

Amitriptyline
Nortriptyline
Doxepin
Haloperidol
Risperidone
Olanzapine
Clozapine
Chlorpromazine

Antihypertensives/Antiarrhythmics

Calcium channel blockers
Clonidine
Verapamil

Antiparkinson Agents

Bromocriptine
Trihexyphenidyl
Benztropine

Opioids

Iron-Containing Products

Ferrous sulfate
Ferrous gluconate

Antihistamines

Chlorpheniramine
Diphenhydramine

Other

Cholestyramine
Loperamide
Sucralfate

Clinical Presentation and Diagnosis

Signs and Symptoms

Painful passage of stools with hard consistency is often described with constipation. In addition to discomfort when stooling, constipation is associated with symptoms such as nausea, abdominal pain, distention, and bloating and can lead to many other complications including rectal fissures, ulcers, rectal prolapse, urinary tract infections, or incontinence. Stool frequency varies with constipation; it should be evaluated more for evacuation of the large colon and change from the patient's normal bowel patterns than for the number of stools per day or week. With functional constipation, the child may exhibit certain behaviors that aid in suppressing the urge to defecate, which include rocking back and forth, standing on tiptoes, or becoming fidgety. The withholding behavior can lead to painful stooling as well as a decreased appetite or food intake because of a full colon.

Diagnostic Criteria

Evaluating stool history and signs/symptoms may be sufficient for diagnosis of functional constipation. The history should include changes in the stool pattern: duration of absence of BM; size, number, consistency, and frequency of stools; any rectal or abdominal pain or bleeding; soiling of underwear; having both diarrhea and hard stools; withholding behaviors; any nausea/vomiting, bloating, or decreased appetite; urinary tract symptoms; and weight loss or change in dietary habits. A complete medication and social history should also be performed.

The physical examination should involve evaluation for abdominal distention, tenderness, presence of hard stool (can be felt on palpation), and physical defects that would be consistent with an underlying cause (e.g., spina bifida) (Reference 31). A digital rectal examination will assist in determining whether a mass or fecal impaction is present. Fecal impaction is defined as a hard mass in the lower abdomen, a dilated rectum filled with a large amount of stool, or excessive stool in the colon as identified by abdominal radiography (Reference 31). Radiographic studies to aid in diagnosis include abdominal radiography and barium enema. Abdominal radiography is helpful to assess stool volume and rectal dilation, and a barium enema is helpful in the diagnosis of strictures, abnormal bowel shape, and even Hirschsprung disease. When a barium enema is performed, the colon is filled with a contrast agent (barium) by a rectal tube. A radiograph is taken, and the barium will block the radiograph, leaving a picture of the colon and revealing any abnormalities. Biopsies may

also need to be performed to assess for Hirschsprung disease or an inflammatory disorder (like Crohn disease). The procedure selected is related to the suspected etiology of the constipation.

Laboratory testing can help rule out potential underlying causes. Thyroid function tests can be evaluated for constipation related to hypothyroidism, magnesium levels on the basic metabolic panel rule out or confirm laxative abuse, and a urine analysis can be performed to test for a urinary tract infection.

In children younger than 1 year, constipation is less common because withholding does not occur. Diagnosis and workup in this population is geared more toward an organic cause. Although the number of stools can vary because of diet (more frequent stools with breastfeeding vs. formula), the patient history and physical examination would vary somewhat from what was previously described. A history of delayed passing of meconium, abdominal distention, bilious emesis (suggesting obstruction), and food avoidance indicate an organic cause like Hirschsprung disease. Evaluation for physical signs of congenital defects, like the presence of a sacral dimple, would point to spina bifida. Understanding age-related causes of constipation can help guide the history and physical examination.

Course and Prognosis of Disease

Constipation, although uncomfortable, is seldom life threatening. However, significant morbidity can occur if progression to chronic constipation is left untreated. Complications of untreated constipation include impaction or obstruction, urinary retention from ureter obstruction, rectal prolapse, and encopresis. Many children with encopresis, defined as the repeated passage of feces in inappropriate places after the developmental age of 4, either have episodes at school or have to wear diaper-type undergarments well past the age-appropriate time. As a result, these patients may undergo social withdrawal, depression, and/or anxiety related to their condition. Medications used to treat depression can compound the problem because they can cause constipation. The social and economic consequences of chronic constipation, including child anxiety and missed days from school or work, should not be overlooked and necessitate the prudent management and prevention of recurrence (References 33 – 39).

Children 2–4 years of age have a higher recurrence rate of constipation than younger infants. About one-third of children with constipation continue symptoms beyond puberty (References 39). In a recent study, 25% of children with functional constipation had symptoms that persisted into adulthood (Reference 40). Several risk factors were identified including older age of onset, delay in time from diagnosis to being seen by a gastroenterologist, and lower defecation history at first presentation. Women were also more likely to relapse than were men. This study suggested quicker follow-up with specialists, especially for those refractory to initial treatment, as a mechanism for relapse prevention (Reference 40).

Treatment

Goals of Therapy

The goal of therapy for constipation is multifactorial and should encompass prevention, alleviation of acute symptoms, and formation of a management plan to avoid recurrence. Because the etiology of constipation differs between infants and children, age should be considered in the management of constipation. The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines outline these differences in the diagnosis and treatment of constipation (Reference 41). The first step in therapy is to provide education on the pathogenesis of constipation, making sure to address the social and psychological reasons for the child's constipation. It should be recognized that constipation is not the result of defiant behavior, and this point may need to be reinforced throughout therapy. Because prevention is the ultimate goal of therapy, changes in lifestyle to facilitate prevention are necessary, including modification of diet. For children, an environment for developing and reinforcing good bowel habits can aid in prevention. Adequate time and a schedule are both key aspects of good bowel habits, but it can take some time to see results. Patience and positive reinforcement are necessary to achieve success.

Alleviating acute symptoms of constipation through both nonpharmacologic and pharmacologic therapies should be the next step in the management of constipation. Acutely, if impacted stool is present, disimpaction should occur, either through manual measures or by pharmacologic management. Disimpaction is necessary before maintenance therapy can begin. When selecting pharmacologic agents, the age of the patient, time to onset of action, and adverse effects should be considered (Reference 41). After acute symptoms are alleviated, any medications used should be weaned to prevent dependence on the medications that would inhibit the development of good bowel habits and act as negative reinforcement for the patient.

Maintenance therapy involving strategies focused on prevention should be initiated once acute alleviation of symptoms has been achieved. This generally involves both nonpharmacologic (dietary interventions and behavioral modification) and pharmacologic (laxative) therapy to ensure regular and complete evacuation of stool. When constipation is associated with medications, the dose should be decreased, if possible,

or concomitant preventive therapy should be initiated. Addressing the three main phases of constipation treatment (acute relief, maintenance therapy, and weaning) is recommended to facilitate successful outcomes.

Nonpharmacologic Therapy

In children, nonpharmacologic therapy with both dietary changes and behavioral management contributes largely to the prevention and maintenance therapy strategies. Increased consumption of fluids and intake of fiber in addition to maintaining a balanced diet of whole grains, fruits, and vegetables should be encouraged. Decreasing the intake of constipating foods like dairy products and starches is also recommended. In infants, juices that contain sorbitol (e.g., prune, pear, and apple juice) are recommended. Fiber can be added in the form of barley malt extract (Maltsupex). In infants, 1–2 teaspoons of barley malt extract can be added to 4 oz of feedings or 2–10 mL per 240 mL of feedings (depending on the formulation) two or three times/day. Barley malt extract is a natural stool softener that may be useful for infants using a bottle because of its unpleasant odor. Corn syrup or sorbitol acts as an osmotic laxative, which can also be used in this population.

Behavioral therapy is an important component of treatment. Regular toilet habits, which include unhurried time on the toilet and maintaining a record of stool frequency, should become part of the daily schedule. Caregivers can institute a positive reinforcement system, or reward system, to record number of stools and foster a relaxed and nurturing environment for the child. Establishing normal stool habits in children through education, behavioral modifications/therapy, and regular toileting practices should be added to any treatment regimen.

One additional nonpharmacologic therapy used in the acute management of constipation is digital disimpaction, although its use is not widely agreed on in the primary care setting and its use would most likely occur if other therapies were unsuccessful.

Pharmacologic Therapy

When selecting appropriate therapy, an underlying cause must be considered. Nonpharmacologic and pharmacologic therapy should be used in conjunction to achieve desired results. The treatment course for constipation can be lengthy. Each phase of treatment (disimpaction and maintenance) has a different duration and expectation of seeing results. For example, impaction can show results within 2–5 days, whereas maintenance therapy can require 3–12 months of treatment to sustain results. Unfortunately, around 50% of children will not respond to initial treatment and will require refractory treatment (Reference 32). Treatment duration and outcomes among children are as different as the child and qualification of constipation.

If fecal impaction is present, disimpaction is the first goal of therapy. Disimpaction can be achieved by several methods. Method and agent chosen depend on patient age, adverse effect profile, route of administration, and severity of impaction because no guidelines or data exist favoring one agent over another. In pediatric practice, agents with the fewest adverse effects, less complicated administration, and high likelihood of adherence are used. Pharmacologic treatment options include glycerin or bisacodyl suppositories, enemas, or oral medications (e.g., mineral oil, polyethylene glycol solutions, magnesium citrate). Both oral and rectal administration can be used for disimpaction. No studies have identified that one route is superior to the other; thus, the choice depends on the child and caregiver. The oral route is less invasive, but adherence to therapy may be difficult. Alternatively, the rectal route is invasive, but it generally has a quick onset. Caution should be used with enema administration to avoid damage to the rectal wall; for this reason, it may not be the first-line option for infants.

Options are generally divided into agents that provide acute relief of impacted stool or maintenance therapy for sustained evacuation or prevention of reimpaction/re-accumulation (Table 4). To disimpact, lubricants such as mineral oil have been widely described in pediatric and adult literature. Mineral oil works by softening stool and preventing water reabsorption. In children younger than 12 years, high doses of up to 15 mL or 60 mL of mineral oil, given by the oral or rectal route, respectively, have been shown to be effective. Too high a dose results in anal leakage, and it should be titrated accordingly. However, mineral oil should not be used in infants because of the risk of aspiration and resulting lipoid pneumonia.

Osmotic laxatives have also been studied for disimpaction in children (Reference 42). Osmotic laxatives prevent the absorption of water or create an osmotic gradient in the gut to pull water into the lumen, thereby increasing the "fluidity" of the stool. Polyethylene glycol is an osmotic laxative with a good safety profile for both infants and children (Reference 43). Electrolyte disturbances should be monitored, however, because osmotic laxatives prevent the absorption of water, and electrolytes follow suit. Polyethylene glycol has also been used in hospital settings for gastric lavage if oral or enema treatment is unsuccessful in disimpaction. In gastric lavage, a nasogastric tube is placed, and the patient is given polyethylene glycol at either 25 mL/kg/hour (max 1000 mL/hour) or 20 mL/kg/hour for 4 hours/day until stools become clear (Reference 41).

Table 4. Pharmacologic Therapy of Constipation

Pharmacologic Agent	Dosing	Onset	Comments
Docusate salts (same dosing for sodium, calcium, potassium salts)	< 3 years: 10–40 mg/day in one to four divided doses 3–6 years: 20–60 mg/day in one to four divided doses 6–12 years: 40–150 mg/day in one to four divided doses > 12 years and adults: 50–400 mg/day in one to four divided doses	12–72 hours	Useful in prevention of constipation, not sole agent for treatment of impaction
Mineral oil	Disimpaction: 30 mL per year of age (max 240 mL) twice daily Maintenance: Oral: 5–11 years: 5–15 mL once daily or divided > 12 years: 15–45 mL/day once or in divided doses Rectal: 2–11 years: 30–60 mL as a single dose > 12 years: 50–150 mL as a single dose	6–8 hours	Should not be used for more than 1 week; caution with use in children < 5 years because of risk of aspiration
Polyethylene glycol (PEG)	MiraLAX oral: child < 20 kg (limited data; studied in children 18 months to 11 years for chronic constipation): 0.25–1 g/kg/day PO divided twice daily (max 17 g/day) > 20 kg: 17 g in 240 mL of water daily GoLytely oral: maintenance: 5–10 mL/kg/day	At constipation dosing, results can be seen after 2 days to 1 week of therapy.	Contraindicated in bowel obstruction; monitor for electrolyte disturbances In general, GoLytely is reserved for older children. Safety of long-term use has not been well established.
Lactulose	Children: 7.5 mL/day after breakfast Adults: 15–30 mL/day to a max of 60 mL/day	Within 24 hours	After discontinuation of therapy, allow 24–48 hours before normal bowel function resumes.
Sorbitol	Oral as 70% solution: Children: 1–3 mL/kg/day in divided doses Adults: 30–150 mL as single dose Enema: 120 mL as a single dose	Within 24 hours	Adjust dose on the basis of the number of daily bowel movements (lactulose and sorbitol similar).
Bisacodyl	Oral: 3–12 years: 5–10 mg or 0.3 mg/kg/day as single dose (max 30 mg/day) > 12 years: 5–15 mg/day as a single dose (max 30 mg/day) Rectal: < 2 years: 5 mg/day as a single dose 2–11 years: 5–10 mg/day as a single dose > 12: 10 mg/day as a single dose	Oral: 6–10 hours Rectal: 15–60 minutes	Not recommended for daily use; may cause considerable abdominal cramping
Sennosides	Syrup (8.8 mg/5 mL): 1 month to 2 years: 1.25–2.5 mL at bedtime (max 5 mL) 2–6 years: 2.5–3.75 mL at bedtime (max 3.75 mL) 6–12 years: 5–7.5 mL at bedtime (max 7.5 mL) > 12 years: 10–15 mL at bedtime (max 15 mL) Tablet (8.6 mg): 2–6 years: ½ tablet at bedtime (max 1 tablet twice daily) 6–12: 1 tablet (max 2 tablets twice daily) > 12 years: 2 tablets (max 4 tablets twice daily)	Oral: within 6–24 hours Rectal: evacuation occurs in 30 minutes to 2 hours	Docusate enhances the absorption of senna.

Pharmacologic Agent	Dosing	Onset	Comments
Magnesium citrate	< 6 years: 2–4 mL/kg/dose given once or in divided doses 6–12 years: 100–150 mL/dose given once or in divided doses > 12 years: 150–300 mL/dose given once or in divided doses	A few hours after oral administration	Used for acute evacuation, not impaction
Magnesium hydroxide	(All liquid milliliter doses are based on 400 mg/5 mL magnesium hydroxide, unless noted otherwise): < 2 years: 0.5 mL/kg/dose 2–5 years: 5–15 mL or 311–622 mg (1 or 2 chewable tablets) 6–11 years: 15–30 mL or 933–1244 mg (3 or 4 chewable tablets) > 12 years and adult: 30–60 mL or 1866–2488 mg (6–8 chewable tablets)	0.5–6 hours	Use with caution in patients with renal impairment. HS or in divided doses.
Glycerin	Neonates: ½ glycerin suppository as needed Children: < 6 years: 1 infant suppository as needed > 6 years 1 adult suppository as needed	15–30 minutes	Not useful for impaction; considered a safe laxative
Phosphate soda enemas	Enema: 2–12 years: 66-mL enema × 1; may repeat × 1 dose. > 12 years and adult: 133 mL enema × 1; may repeat × 1 Oral: 5–9 years: 5 mL PO × 1 dose 10–12 years: 10 mL PO × 1 dose > 12 years and adult: 20–30 mL PO × 1 dose	Rectal: 2–5 minutes Oral: 3–6 hours	For oral administration, mix 1:1 with water. Separate doses by 10–12 hours. Contraindicated in renal failure. May cause electrolyte disturbances

Takemoto CK, Hodding JH, Kraus DM. Pediatric & Neonatal Dosage Handbook, 18th ed. Hudson, OH: Lexi-Comp, 2011 (Reference 19).
The Constipation Guideline Committee. Evaluation and treatment of constipation in infants and children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2006;43:e1–13 (Reference 41).
Payton KSE. Gastroenterology. In: Tschudy MM, Arcara KM, eds. The Harriet Lane Handbook: A Manual for Pediatric House Officers, 19th ed. Philadelphia: Elsevier Mosby, 2012:295–8 (Reference 46).
HS = at bedtime; PO = orally.

Other osmotic agents that have been used for disimpaction in children, but that have more limited data in pediatric patients, include magnesium citrate, magnesium hydroxide, lactulose, and sorbitol. Magnesium citrate is an osmotic cathartic that is not commonly used for disimpaction, particularly in those younger than 2 years because of their susceptibility to magnesium toxicity. Toxicity can lead to electrolyte disturbances including hypermagnesemia, hypophosphatemia, and hypocalcemia and their sequelae. Magnesium hydroxide can also be used, but it is indicated more for maintenance therapy. Magnesium hydroxide induces the release of cholecystokinin, which stimulates the secretion of water and motility. Like the citrate salt, it should not be used in infants because magnesium toxicity can occur. In the presence of renal dysfunction, magnesium accumulation can occur, especially when in combination with aluminum salts; thus, it should be avoided in these patients. Magnesium salts can cause considerable cramping and gas; they are therefore less well tolerated in the pediatric population. Lactulose and sorbitol are both osmotic laxatives composed of indigestible sugars. They are generally well tolerated for long-term use, but data are limited on their use for disimpaction. Lactulose and sorbitol cause flatulence and abdominal cramping and should be titrated to balance efficacy with these adverse effects. Sorbitol enemas have also been used for drug overdoses, but they are not routinely used for fecal impaction.

Enemas effective for fecal impaction include phosphate soda and saline enemas. However, they are generally reserved for children older than 2 years. Phosphate soda is an osmotic enema and should not be used in renal impairment because accumulation can occur. The use of soapsuds, tap water, or magnesium enemas is not recommended because of the associated toxicities, including bowel perforations, necrosis, or even water intoxication (References 29, 41).

Stimulant laxatives, including glycerin, bisacodyl, and senna, are also effective in the treatment of fecal impaction in children. Glycerin suppositories are perhaps most widely used in the neonatal and infant populations. Glycerin works through osmotic properties, but the direct rectal stimulation often produces the desired results. A stellar safety profile and variety of available dosing sizes make glycerin a good choice for infants.

However, glycerin's effectiveness may be decreased once rectal distention has occurred (References 44, 45). Bisacodyl, a stimulant, can be given orally or rectally in older children (not indicated in children younger than 2 years). It works by stimulating the nerves in the colon to cause movement as well as increase the secretion of water and chloride. Orally, it has been used for disimpaction, usually in conjunction with other therapies. Rectal use is generally not as effective because the suppository is usually inserted into the middle of the stool, rather than where it can come into contact with the mucosa, and will not have the desired action. Abdominal cramping, hypokalemia, and diarrhea have all been associated with bisacodyl use. Senna is another stimulant laxative that works by stimulating colonic nerves to produce peristalsis, or movement, in addition to preventing water and electrolyte absorption to soften stools. Senna has a quicker onset of action than bisacodyl (1–3 hours vs. 6–12 hours). Senna is often used in combination with stool softeners, mainly docusate. One unique adverse effect is the presence of melanosis coli. Melanosis coli is a benign darkening of the colon that generally improves within 4–12 months after senna discontinuation (Reference 41). As stated earlier, refractory constipation warrants further workup for an underlying disorder, including performing a barium enema or rectal biopsy. If an underlying disorder such as Hirschsprung disease is discovered, or if a patient is unsuccessfully disimpacted, surgery may be warranted to remove the area of bowel that is not functioning and/or the removal of stool. An ostomy, or surgically created opening from the intestines to the outside of the body, may be needed after surgery. Having an ostomy requires special care and diet considerations because absorption may be affected.

In general, once disimpaction occurs, maintenance therapy involves the combination of dietary and behavioral changes, together with lubricants or osmotic laxatives (or a combination of the two), if pharmacologic therapy is necessary. In infants, the maintenance stage can usually be maintained with a stool softener alone. Toddlers—stool-withholder experts—may require both stool softeners (e.g., docusate sodium) and stimulants at the beginning of the maintenance phase. Docusate works by reducing the surface tension of the oil/water interface of stool, causing increased absorption of water in the stool and ultimately softening stools (much like a soap acts on changing oil and water interfaces) (Reference 46). Docusate is available as several salts including sodium, calcium, and potassium that are considered interchangeable. Table 4 provides dosing for medications used for the treatment of constipation.

Monitoring of Therapy

The ultimate goal of therapy is having a regular stool pattern and complete evacuation of stool. It should be understood that the use of laxatives is to promote comfortable evacuation, not as a medication to induce stooling. Relying on laxatives to evacuate stool can lead to laxative abuse. Therefore, incorporating all of the types of therapy previously discussed is the most appropriate approach to therapy (References 29, 32, 41).

If impaction is present, disimpaction must occur before other therapy can begin. When evaluating the effectiveness of therapy, the clinician should consider the time of onset for the agent. The type, or class, of agent selected will produce results at different times, and adequate time for these agents to work should be granted before adding or changing therapy (see Table 4). Complete evacuation can take 2–5 days. If complete evacuation is not achieved within this time, admission to the hospital for oral gastric lavage with a polyethylene glycol solution is warranted. The patient should have a complete evacuation of stool after treatment, and maintenance therapy should begin to reinforce good bowel habits and maintain evacuation to restore normal bowel tone.

During the maintenance phase, stool softeners and, periodically, stimulants, are used to ensure consistent complete evacuation and the return of normal bowel tone. This phase can take from 2 to 6 months. Stimulants and a dependence on laxatives for stooling should be evaluated by the practitioner to prevent dependence.

Weaning of therapy is the final step in the therapeutic plan. It is important to remember that "normal bowel function" is different for each patient, and a return to the patient's "normal" should be sought when evaluating the effectiveness of therapy. Weaning agents should be done gradually, and some patients may require regular use of stool softeners even after normal bowel tone returns. If the patient is taking daily medication, the medication may be weaned by going to every-other-day therapy for 1 month, followed by every 3 days for 1 month until complete evacuation occurs on a regular basis. During this phase, dietary and behavioral therapy should continue. To prevent impaction, a stimulant laxative may be administered if the child does not stool for more than 3 days. Maintaining a stool diary and reinforcement of good bowel habits may be necessary to recognize the early signs of recurrence including feeling of incomplete evacuation, return of stool-withholding behaviors, or irregular stooling. Throughout therapy, monitoring for drug-specific adverse effects and balancing that with efficacy should be considered. Introduction of medications or dietary changes that may cause constipation should also be monitored and considered if symptoms of recurrence are present. The expectation of clinicians

and caregivers alike should be that achieving therapeutic goals can take months; even with appropriate therapy and management techniques, recurrence rates have been described in up to 50% of cases (Reference 32). If the goals cannot be achieved after adequate time and therapy attempts, a specialist may be required to complete a further workup for an underlying etiology or to assist with management techniques.

Conclusions

Diarrhea and constipation are common disease states in children. Although diarrhea is a leading cause of morbidity and mortality worldwide, rehydrating with appropriate fluids, like ORT, and monitoring hydration status have been shown to considerably affect survival (References 14–18). When treating diarrhea, if an underlying etiology can be identified, treatment should be tailored. Many times, an exact cause is unknown, but hydration management principles remain the same. Although pharmacologic therapy is not indicated as a cure for most cases of acute diarrhea, treatment with medications has or may have a place for refractory cases and for the management of chronic diarrhea. Treatment should be individualized and reassessed often. Likewise, constipation management should be individualized and guided by the underlying cause, either organic or nonorganic. It is important to identify any underlying etiology because constipation is often recognized as a symptom, so treatment can be specific to the cause. Most cases are functional in origin and should be managed with diet and behavioral and pharmacologic therapy. Ultimately, the goal is to maintain complete evacuation and restoration of good bowel tone and habits. Therapy involves both an acute and maintenance approach and should be continuously monitored for changes in efficacy to step up or step down treatment. The risk of medication abuse, resulting in lack of efficacy, should also be evaluated in the treatment regimens. Understanding the cause of the patient's constipation, providing positive reinforcement of good bowel habits, and employing safe and effective use of pharmacologic therapy can help decrease the likelihood of relapse or future poor outcomes so often seen with chronic constipation. For both diarrhea and constipation, completion of a careful history, patient evaluation, and close follow-up will ensure appropriate selection and monitoring of therapy.

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CHAPTER 18

Irritable Bowel Syndrome

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Learning Objectives

1. Discuss the epidemiology of irritable bowel syndrome (IBS).
2. Understand the pathophysiology of IBS.
3. Recognize the signs and symptoms of IBS.
4. Discuss the diagnosis and classifications of IBS.
5. Explain the overall management and treatments associated with IBS.
6. Discuss monitoring the efficacy and toxicity of agents used in the treatment of IBS.

Abbreviations in This Chapter

FGID	Functional gastrointestinal disorder
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant IBS
IBS-D	Diarrhea-predominant IBS
RAP	Recurrent abdominal pain

Introduction/Overview

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) characterized by chronic abdominal pain or recurrent abdominal pain (RAP) and altered bowel habits in the absence of an organic cause. In children and adolescents, chronic abdominal pain and RAP are two of the most common concerns presented to health care practitioners (References 1, 2). Chronic abdominal pain and RAP are defined as pain without a determined cause that occurs during a 3-month period. Children with a history of RAP are at an increased risk of developing IBS in young adulthood (Reference 3). The pathophysiology of IBS is likely multifactorial. The symptoms of IBS can help diagnose and classify IBS and thus guide treatment. Treatment will be individualized to the patient's symptoms, with a goal of improving the patient's quality of life.

Epidemiology

Irritable bowel syndrome is one of the most common gastrointestinal (GI) disorders for which patients seek medical treatment. Recurrent abdominal pain, or functional abdominal pain, is the main functional bowel disorder seen in children and has been linked to IBS. Recurrent abdominal pain occurs in about 10% of children and adolescents. In a historical study of 1000 school-aged children, RAP was uncommon among children 5 years and younger. Until age 9, boys and girls are equally affected by RAP. After 9 years, girls are 1.5 times more likely to be affected, with the overall incidence peaking at 10–12 years (Reference 1). The incidence of IBS in children has not always been clearly determined. Now, however, with specific pediatric criteria for IBS, the children once classified as RAP can then be divided further into two groups. Functional abdominal pain accounts for 35% of patients with RAP, and IBS accounts for 65% of patients with RAP (Reference 4). About 6% of middle school and 14% of high school students report IBS-like symptoms. Even though in adults, IBS affects more women than men, in children boys and girls are affected equally (Reference 2).

Pathophysiology

The pathophysiology of IBS is poorly understood, although more theories are emerging. There is no single cause for IBS, but it is likely multifactorial. Irritable bowel syndrome is a biopsychosocial disorder with three primary mechanisms: altered motility, altered sensation of the intestine, and psychosocial factors. Most data on the pathophysiology of IBS are seen from studies of adults. The exact mechanism is unclear in most children who have no identifiable organic cause. Studies have suggested chronic stress, genetic factors, bacterial overgrowth, postinfectious, serotonergic disorders, and altered inflammatory response as potential causes.

Altered motility is described as a group of small bowel contractions causing abdominal pain with abnormal GI transit times. There is an increase in the frequency and irregularity of luminal contractions that can be prolonged in IBS. The intestinal transit time can be accelerated by increased contractions in patients with diarrhea-predominant IBS (IBS-D). In contrast, the transit time can be delayed with fewer high-amplitude contractions, as seen with constipation-predominant IBS (IBS-C) (Reference 5). Altered motility used to be thought to be the main contributor in IBS, but current evidence shows that visceral hypersensitivity plays a bigger role.

Children with IBS have an association with visceral hypersensitivity or altered sensation of the intestine. A distention of the lumen of the gut does not usually produce pain in control individuals but can cause pain in a

patient with IBS (Reference 6). Visceral hypersensitivity appears to be from an alteration in communication between the enteric nerves of the intestine and the gut bacteria and the central nervous system (Reference 7). Another term that has been used is *visceral hyperalgesia*. This is a heightened awareness of sensations that can be perceived as painful and not felt or even expressed as pain by other children. It has been recognized in children with IBS to have a higher association with rectal hyperalgesia. After rectal balloon distention, children with IBS perceived rectal pain at a lower threshold compared with other children. It is thought to develop from hyper-excitable neurons in the dorsal horn. This hypersensitivity of nerves in the gut is triggered by bowel distention and bloating (References 6, 8).

The psychosocial component in the pathophysiology of IBS can be an important factor. Some studies show a higher level of anxiety and depression in children with IBS compared with other children. It is often difficult to distinguish whether illness and pain-causing anxiety or anxiety and stress is the primary cause of IBS. Children who meet the criteria for IBS associate stressors with an increase in their abdominal pain (Reference 3). In addition, these children are less confident in their ability to deal with stress and less likely to use coping strategies. The psychological state of the mother is related to greater use of health care services for their children's abdominal pain. In children with RAP, an association was found with their mothers' history of anxiety and depression (References 9, 10). This may suggest a genetic component to IBS. Although no specific IBS gene has been identified, familial studies link positive family history as a predictor for IBS. A genetic predisposition to IBS in children is also observed, with an increased correlation of IBS with identical twins versus fraternal twins (References 11–14). It is unclear whether this relationship is caused by genetics or similar environmental factors.

Gut flora is also altered in patients with IBS compared with controls (Reference 15). The altered gut flora may develop after an enteric viral, bacterial, or parasitic infection (References 16–18). It can also be referred to as postinfectious IBS and may have an increased correlation in patients with a history of anxiety (Reference 19). In one study, 36% of children with a history of an acute bacterial gastroenteritis developed the abdominal pain symptoms seen with FGIDs. In this group, 87% of the children's symptoms met the criteria for IBS (Reference 20). Even after the infection has resolved, IBS symptoms can persist for many years (Reference 17).

Neurotransmitters such as cholecystokinin, substance P, and 5-hydroxytryptamine (serotonin), found in the brain and intestines, help regulate cortical centers with visceral afferent sensation and intestinal motor function. They can work on the areas of the brain and GI system that have various effects on GI motility, emotions, and pain. Serotonin is a monoamine neurotransmitter found mainly in the GI tract. It plays an important role in gut signaling and function. Serotonin regulates GI motility, secretion, and intestinal sensation. After a meal, elevated levels of serotonin have been seen in patients with IBS-D, whereas decreased levels are seen in patients with IBS-C (References 21, 22).

Intestinal inflammation and possibly mast cells may also play a role in IBS (Reference 23). The mast cells are involved in normal immune function and release inflammatory mediators such as histamine and tryptase in response to antigen stimuli, especially in allergic diseases. Studies have found an increased number of mast cells in the GI tracts of patients with IBS. These mast cells have also been shown to be near sensory nerves, which can lead to the symptoms of abdominal pain and hypersensitivity seen with IBS (References 24–26). The role of inflammation in the etiology of IBS symptoms in children requires further study.

Clinical Presentation and Diagnosis of IBS

Irritable bowel syndrome can be characterized as an FGID associated with altered bowel movements and pain (Reference 27). These alterations in bowel movements can occur with increased or decreased frequency. The pain, which is usually poorly defined, is characterized as periumbilical pain. It can last for less than 1 hour and can be unrelated to meals, activity, and stool patterns. Typically, children 3–10 years of age report "belly pain" as the most frequent location, whereas children 11–17 years of age most often report headaches in combination with abdominal and back pain (Reference 28). The diagnosis of IBS is usually symptom-based because of the lack of biochemical or physical markers. Therefore, a thorough history and physical examination are important and should include a nutritional assessment and inquiry into the psychosocial history of the child and family. Established criteria should be used in the diagnosis, while excluding organic disease (Box 1). Irritable bowel syndrome in children is usually not described before a certain age because of the inability of children to report symptoms. In general, it can be diagnosed in children 4–18 years of age.

The Committee on Childhood Gastrointestinal Disorders defines IBS as at least 12 consecutive or nonconsecutive weeks in the past 12 months of abdominal pain with two of the following three features: (1) pain relieved with defecation, (2) onset associated with change in stool frequency, or (3) onset associated with change in stool appearance. The committee also include that there should be no structural or metabolic abnormalities to explain the symptoms (References 30, 31). The Manning and Rome criteria provide the standard

definitions for IBS in adults and children. The Manning criteria, introduced in 1978, includes abdominal pain relieved by defecation, more frequent stools or looser stools at the onset of pain, visible abdominal distention, passage of mucus, and sensation of incomplete evacuation. The Rome III criteria added the duration and frequency of the stools and symptoms (Table 1). In adults, the bowel patterns are then subdivided into three categories: IBS-D, IBS-C, or mixed IBS. Similar patterns are also recognized in children (References 30, 32–37) (Box 2; Table 2).

The American College of Gastroenterology (ACG) IBS Task Force recommends that, in the typical patient with IBS, routine diagnostic testing and colonoscopy not be done unless alarm symptoms are seen (Reference 38). Alarm symptoms can include the presence of blood in the stool, involuntary weight loss, decline in linear growth, significant vomiting, chronic severe diarrhea, persistent pain away from the umbilicus, unexplained fever, family history of inflammatory bowel disease, or abnormal physical examination findings (References 27, 36) (Box 3).

Typically, laboratory testing and other diagnostic testing in patients with IBS are normal. Even though they are not always done in patients with IBS, they can help exclude organic causes. A complete blood cell count with differential, C-reactive protein, and erythrocyte sedimentation rate can help confirm an infectious or inflammatory process. Stool studies are not typically done, but they can exclude bacterial, protozoan,

Box 1. Possible organic causes of abdominal pain.

Constipation
Carbohydrate malabsorption
Pelvic inflammatory disease
Gastroesophageal reflux disease (GERD)
Gastrointestinal ulcers
Lactose intolerance
Parasitic infections
Muscle and/or bone pain
Urinary tract infection
Inflammatory bowel disease
(Crohn disease or ulcerative colitis)
Menstruation
Endometriosis

References 27, 29.

Box 2. IBS subtyping classifications.

Constipation-predominant IBS (IBS-C)
- ≥ 25% of bowel movements hard or lumpy stools (Bristol Stool Form Scale 1–2)
- ≤ 25% of bowel movements loose/mushy or watery stools (Bristol Stool Form Scale 6–7)

Diarrhea-predominant IBS (IBS-D)
- ≥ 25% of bowel movements loose/mushy or watery stools (Bristol Stool Form Scale 6–7)
- ≤ 25% of bowel movements hard or lumpy stools (Bristol Stool Form Scale 1–2)

Mixed IBS (IBS-M)
- ≥ 25% of bowel movements hard or lumpy stools (Bristol Stool Form Scale 1–2)
- ≥ 25% of bowel movements loose/mushy or watery stools (Bristol Stool Form Scale 6–7)

Reference 35.
IBS = irritable bowel syndrome.

Table 1. Manning and Rome III Criteria for IBS Diagnosis

Manning Criteria	**Rome III Criteria**[a]
Abdominal pain	Recurrent abdominal pain or discomfort[b]
Plus two or more of the following:	*Plus two or more of the following:*
Relieved by defecation	Improvement with defecation
More frequent stools at onset of pain	Onset associated with a change in frequency of stool
Looser stools at onset of pain	Onset associated with a change in form (appearance) of stool
Visible abdominal distention	
Passage of mucus	
Sensation of incomplete evacuation	

[a]Occurred at least 3 days/month in the past 3 months, with symptom onset at least 6 months before diagnosis.
[b]Discomfort means an uncomfortable sensation not described as pain.
IBS = irritable bowel syndrome.
References 32, 34.

Table 2. Bristol Stool Form Scale

Type	Description
1	Separate hard lumps, like nuts (hard to pass)
2	Sausage shaped but lumpy
3	Like a sausage but with cracks on its surface
4	Like a sausage or snake, smooth and soft
5	Soft blobs with clear-cut edges (passed easily)
6	Fluffy pieces with ragged edges, a mushy stool
7	Watery, no solid pieces, entirely liquid

Reference 37.

Box 3. Alarm symptoms.

- Involuntary weight loss
- Decline in linear growth
- Presence of blood in stool
- Significant vomiting or diarrhea
- Persistent right upper or lower quadrant pain or tenderness
- Unexplained fever
- Family history of inflammatory bowel disease
- Localized fullness or mass effect
- Hepatomegaly or splenomegaly
- Tenderness over the spine
- Perianal abnormalities
- Abnormal or unexplained physical findings

References 27, 36.

or parasitic causes of abdominal pain, such as giardiasis. In addition, a complete metabolic panel that includes a liver function test and amylase or lipase can help exclude metabolic causes or pancreatitis. Depending on the clinical course, some patients will have a radiologic evaluation, such as abdominal ultrasonography or computed tomography (CT), or an upper GI series with small bowel follow-through to evaluate structure. Some patients may also require an endoscopy to further evaluate structure and to exclude organic disease.

Prognosis/Mortality/Morbidity

Irritable bowel syndrome is not life threatening, does not progress to other diseases, and does not damage the bowel. However, IBS can cause discomfort and distress that affects a child's daily activities and quality of life. Long-term studies suggest that abdominal pain and GI upset persist into adulthood. Adults with IBS recall having a history of childhood abdominal pain, with more physician visits and more school absences compared with other children. In addition, they report more headaches and more overall bowel symptoms (References 39–41). In a 12-year follow-up study, children with stomachaches who often used the school clinic were shown as adults also to use medical services frequently (Reference 42). The pain interferes with children's daily activities such as school, and often, the quality of life of these children is poor. They seem to have lower physical, emotional, social, and school functioning than other children and a quality of life similar to children with organic GI disease (References 4, 43).

Management

The management of IBS, which has many components, is dictated by illness severity, predominant symptoms, and patient preferences. It is important to have a positive patient and health care provider relationship. In a national survey of patients with IBS, the most desirable relationship provided a patient-centered focus; a source for information and questions, listening, and support; and hope (Reference 44). When the child's biopsychosocial and clinical needs are treated, parents report higher satisfaction rates with overall care and are more receptive to treatments (Reference 45). The primary treatment goals are to return to normal function with effective reassurance and to reduce or eliminate symptoms (Reference 27). Educating the family can play a vital role in the care of these patients. Parents need to understand that the symptoms cause pain that is not life threatening but that can interfere with the child's life. Parents should acknowledge the pain but encourage daily activities and school attendance (Reference 46).

Nonpharmacologic Management

Cognitive behavioral therapies, psychotherapy, hypnotherapy, and stress management can reduce the symptoms of IBS (Reference 38). Patients who understand their symptoms to be mainly psychological will benefit from cognitive behavioral therapies. For patients with increased anxiety or depression, these therapies seem less helpful (Reference 47). Many of these therapies affect the physical aspects of IBS as well as help give the child the ability to self-manage symptoms. The overall goals are to support families and help children identify psychological triggers, learn better independent coping and problem-solving skills, and change behavior. Cognitive behavioral therapies can include focusing on relaxation or distraction; keeping a diary of symptoms, triggers, and feelings; gradually facing avoided daily activities; and using positive and negative reinforcement (References 48, 49). The American Academy of

Pediatrics guidelines for chronic abdominal pain concluded that these therapies are useful in the short term for improving pain (Reference 27). Other studies have concluded that these approaches decrease pain in 70% to 90% of children and sometimes help reduce school absences and medication use. These studies used several interventions and involved the children in weekly therapy sessions ranging from 4 to 12 weeks (References 50–53).

Diet

Dietary changes have been suggested in children with IBS because most patients with IBS believe that diet plays a role in their symptoms. A survey of adult patients with IBS showed that they believed they should avoid fatty foods, milk products, carbohydrates, caffeine, and high-protein foods. The patients also felt that their diet should include increasing their fiber intake and eating smaller meals. But the overall evidence for food avoidance remains unproven (References 54–56). Recommendations from the ACG IBS Task Force are not to exclude food from patients, except for purposes related to clinical trials. Patients with IBS have a higher prevalence of lactose intolerance. If the child's symptoms are consistent with those of lactose intolerance (e.g., cramping pain and bloating after milk and milk-containing foods), then eliminating lactose from the child's diet can be helpful. Children can avoid milk and milk products or use lactase enzyme replacements. Whether lactase avoidance can decrease the pain in children is unproven. A food diary is recommended to correlate foods with symptoms and to minimize dairy products at the onset or exacerbation of IBS symptoms (Reference 38). Avoiding other trigger foods (high fat or gas producing), drinks (caffeinated), and medications (nonsteroidal anti-inflammatory drugs) that can aggravate symptoms can be helpful for some patients. It may be beneficial to exclude gluten in patients with IBS-D who also have celiac disease markers, such as celiac disease–associated serum immunoglobulin G and *HLA-DQ2* allele expression. One study found that symptoms improved in 60% of patients with IBS-D with positive celiac serologies versus 12% in those with negative serologies (Reference 57).

Nutritional status should always be considered in children, especially with IBS-D. If oral intake is inadequate or if malabsorption occurs, enteral feedings or even parenteral nutrition may be considered, although it is not often needed. Sufficient calories should be provided to maintain growth and even allow catch-up weight gain. Micronutrient and vitamin supplementation should also be considered in patients with IBS, with a focus on zinc, vitamin A, folic acid, copper, and selenium (Reference 58).

Treatment

Constipation-Predominant IBS

Fiber and Bulking Agents

Although it is unproven, increasing fiber in a child's diet may improve symptoms, especially those with a constipation component. Fiber can help the stool hold onto water, promote gel formation to provide lubrication, provide bulking of the stool, and bind bile (Reference 59). Fiber can produce bowel movements that are more regular and decrease abdominal pain by softening the stool and increasing colonic transit. Fiber can be found in a well-balanced diet, including fruits and fruit juices, vegetables, and whole-grain cereals and breads. Children may also try high-fiber cookies or crackers, granola bars, or dried fruit. Fiber supplementation with soluble fiber, such as psyllium, is the first-line treatment in IBS-C. Fiber supplements are available in several forms, including powdered fiber that can be mixed in juice or made into popsicles, wafers, or chewable tablets. Fiber supplements are usually given two times/day and must be taken with a sufficient amount of water. Overall, the daily intake of water should be sufficient, with younger children drinking 2–4 glasses of water and older children drinking at least 6 glasses of water. To decrease the adverse effects of flatulence and bloating, supplementation should be a gradual process in which fiber intake is slowly increased and stool output and frequency are monitored. Supplements can improve global IBS symptoms and reduce symptom severity, but they do not improve quality of life (References 36, 60, 61) (Table 3). The additional fiber may exacerbate some symptoms in children; thus, supplements must be used with caution, especially in children who tend to withhold stools or who have chronic constipation. Fiber can increase stool bulk and cause greater distension of the rectum and colon.

Laxatives

Laxatives are commonly used to treat chronic constipation. However, whether using osmotic laxatives (e.g., polyethylene glycol [PEG], lactulose) or stimulant laxatives (e.g., bisacodyl, senna), their efficacy in IBS has not been shown. The goal of laxative therapy is to achieve one soft stool per day. This, together with behavior therapy, may take weeks, months, and sometimes years to achieve. A study of adolescents with IBS-C taking PEG alone or in combination with tegaserod showed an increase in stool frequency, but abdominal pain remained unchanged (Reference 34). In this study, the children were initially cleaned out with bisacodyl suppositories and then given PEG 17 g in 8 oz of fluid daily 1–2 hours before supper. Most laxatives seem equally efficacious, so choosing one may be based on

Table 3. Treatment Options for IBS-C and IBS-D

			Common Adverse Effects
IBS-C			
Fiber	Fruits, vegetables, whole grains Psyllium	Child's age plus 5–10 g/day Children 6–11 years: 1.25–15 g/day in two or three divided doses Children > 12 years: 2.5–30 g/day in two or three divided doses	Rectal distension Colonic distension
Laxatives			
Osmotic	Polyethylene glycol (PEG) (powder)	1 g/kg/day in two or three divided doses	Bloating Flatulence
	Lactulose (syrup)	1–3 mL/kg/day in two or three divided doses Max of 60 mL/day	
Stimulants	Senna (syrup, granules, and tablets)	2–6 years old: 2.5–7.5 mL/day in two divided doses 6–12 years old: 5–15 mL/day in two divided doses	Abdominal cramping Discoloration of stool and urine
	Bisacodyl (tablets, suppositories)	≥ 2 years: 0.5–1 suppository or 5- to 10-mg tablet/dose	Abdominal cramping
IBS-D			
Antidiarrheals	Loperamide	0.08–0.24 mg/kg/day in two or three divided doses (max of 2 mg/dose)	Abdominal distension Abdominal cramping Urinary retention

IBS-C = constipation-predominant irritable bowel syndrome; IBS-D = diarrhea-predominant irritable bowel syndrome.
References 62–66.

the child's preference, cost, ease of administration, and effectiveness for the individual child. Laxative use may be limited by the adverse effects of bloating and flatulence with the osmotic laxatives and abdominal cramping with the stimulant laxatives. Stimulant laxatives are not recommended for prolonged use (Table 3).

Tegaserod

Tegaserod, a selective partial agonist of the serotonin-4 receptor for serotonin, has been used in IBS-C in adults. By activating these receptors, tegaserod leads to increases in peristaltic activity and decreases in visceral hypersensitivity. In adolescents, it decreases the pain associated with IBS when used with a laxative. The global assessment scores for constipation, pain, and bloating were significantly improved without serious adverse effects (Reference 62). In 2007, tegaserod was removed from the market because of the cardiovascular risks reported in postmarketing surveillance. Currently, in the United States, tegaserod is only available under a U.S. Food and Drug Administration (FDA) emergency drug protocol for patients older than 55 years. It has been argued that tegaserod would still be a valuable drug in children with IBS. Most adverse events were seen in adults with preexisting cardiovascular disease or risk factors. But because of the restrictions on the drug, its use in pediatric patients would warrant additional randomized controlled trials (References 62, 67).

Lubiprostone

Lubiprostone is indicated for the treatment of IBS-C in women 18 years and older, but it is being evaluated in a phase IV trial of children and adolescents. The trial is an open-label study assessing the safety and efficacy of lubiprostone in functional constipation in children younger than 18 years and weighing at least 12 kg. Lubiprostone stimulates intestinal fluid secretion by serving as chloride channel activators and increasing intestinal motility. It helps facilitate the passage of stool and alleviate symptoms associated with constipation. Preliminary results showed a doubling of spontaneous bowel movements during a 4-week treatment of constipated children. Moreover, straining and pain were reduced, and stool consistency was improved. There was

also a reduction in the use of rescue medications (e.g., oral laxatives, suppositories, enemas). Lubiprostone has the potential to be a useful product for children with constipation symptoms, but again, further studies are required to confirm this (References 68, 69).

Diarrhea-Predominant IBS

Antidiarrheal Agents

Antidiarrheal agents such as loperamide improve stool characteristics. Loperamide is an opioid-receptor agonist that acts on receptors in the large intestine to slow colonic transit. Loperamide can also improve diarrhea by decreasing stool frequency and incontinence, but it has not been shown to effectively decrease IBS symptoms or abdominal pain (Reference 38) (Table 3).

Abdominal Pain Associated with IBS

Antispasmodics

Activation of cholinergic receptors in smooth muscle may be associated with abdominal pain in IBS. Pain may be caused by a smooth muscle spasm, and antispasmodics (e.g., hyoscyamine, dicyclomine, peppermint oil) are thought to be helpful. Hyoscyamine and dicyclomine have anticholinergic effects on the GI smooth muscle. In the adult population, there is consistent evidence for their use, but studies of pediatric patients with IBS are lacking. Hyoscyamine and dicyclomine have been used in children for short-term relief. However, caution should be used with prolonged use because they can cause other anticholinergic adverse effects, such as urinary retention, constipation, tachycardia, and drowsiness. The active ingredient in peppermint oil, menthol, has calcium channel blockade properties that decrease smooth muscle spasms in the ileum and colon. A small randomized placebo-controlled trial of peppermint oil in 42 children with IBS was performed for 2 weeks. The study found that 76% of the children reported improvements in IBS symptoms with no changes in stool pattern or consistency. The ACG IBS Task Force recommends the use of any antispasmodic for short-term relief but states that long-term efficacy and safety have not been shown (References 38, 70).

Antidepressants

Antidepressants have been used at low doses to improve sleep, improve bowel transit times, and decrease visceral hypersensitivity in children and adults. Through their anticholinergic effects, they are thought to reduce pain perception, improve sleep patterns, and modulate the GI tract (Table 4). Patients with comorbid depression or anxiety also show improvement. In 2004, the FDA issued a formal black box warning of antidepressant use in children and adolescents for increases in suicidal ideations and behavior. Further studies have shown no evidence of increased suicidal risk, but suicidal ideations did increase. Overall caution should be taken when prescribing antidepressants for children, together with a close monitoring of the adverse effects in the first few weeks of initiating the medication.

Table 4. Treatment Options for Abdominal Pain Associated with IBS

			Common Adverse Effects
Anti-spasmodics	Hyoscyamine (elixir, tablets)	2–12 years: 0.0625–0.125 mg per dose every 4 hours as needed (max 0.75 mg/day) > 12 years: 0.125–0.25 mg every 4 hours as needed (max 1.5 mg/day)	Constipation Dry mouth Urinary retention Tachycardia
	Dicyclomine (syrup, tablets)	5–10 mg per dose three or four times/day	
Anti-depressants			
Tricyclic	Amitriptyline (tablets)	< 35 kg: 10 mg at bedtime > 35 kg: 20 mg at bedtime	Sedation Weight gain
SSRIs	Citalopram (solution, tablets)	Initial 10 mg, second week 20 mg, if no improvement by fourth week, 40 mg; daily dosing	Sedation Agitation Nausea/vomiting Withdrawal symptoms with abrupt discontinuation

IBS = irritable bowel syndrome; SSRI = selective serotonin reuptake inhibitor.
References 63, 71, 73, 74.

Tricyclic antidepressants (e.g., amitriptyline) and SSRIs (selective serotonin reuptake inhibitors) (e.g., citalopram) have been studied in children with IBS. Tricyclic antidepressants have been used in IBS-D because of their anticholinergic effects of causing constipation. In two pediatric randomized placebo-controlled trials, amitriptyline was given at 10 mg, 20 mg, or 30 mg (based on weight) for 4–8 weeks of therapy. Amitriptyline was seen to improve the overall quality of life from baseline and reduce anxiety scores in patients with IBS. Most of the patients reported feeling better but had inconsistent reports of improvement in pain, with no improvement in other IBS-related symptoms (References 71, 72).

Serotonin is an important neurotransmitter in the GI tract; SSRIs may be beneficial for IBS. More than 80% of the body's serotonin stores are found in the GI tract and are thought to regulate GI motility and visceral pain. Selective serotonin reuptake inhibitors have been used in IBS-C for their tendency to cause diarrhea, but well-controlled randomized pediatric trials are lacking. In a prospective, open-label study of children with functional RAP, citalopram was initiated at 10 mg/day and could be increased to 40 mg/day for 12 weeks. In 84% of the children, abdominal pain, anxiety, depression, and daily function improved (References 71, 73–75). Antidepressant use in children with IBS may only be beneficial in a few, particularly those with anxiety or other psychological states (Reference 36). Overall, the use of antidepressants in IBS may be promising, but their efficacy and safety must still be established in the pediatric population.

Anti-inflammatory Agents

Because of the role of inflammation in IBS, anti-inflammatory agents have been studied in adults. Prednisolone, when used in a postinfectious IBS trial, did not prove helpful in the patients' symptoms (Reference 76). Another anti-inflammatory agent commonly used in inflammatory bowel disease, mesalamine, has been studied. Although it has not been shown to reduce abdominal pain and bowel habits, it causes inhibition of mast cells in the GI tract and improves overall IBS symptoms. Data are limited regarding the use and efficacy of anti-inflammatory agents in adults with IBS. Although no trials or data in pediatric IBS exist, this may be an area for study (Reference 77).

Probiotics

Probiotics are live microorganisms that can provide beneficial health effects to the host. An imbalance of the normal gut flora has been linked to dysmotility and visceral hypersensitivity. Probiotics are thought to restore the bacteria balance in the gut by creating a better mucosal barrier in the intestine or changing the inflammatory response of the intestines. Studies suggest that probiotics provide a moderate benefit in children by decreasing pain, but they do not appear to decrease the frequency of pain (References 78–80). Nor has the specific strain of probiotic been determined. Most studies use *Lactobacillus* strains, but inactive *Escherichia coli* bacteria have also been used with some success. With *E. coli* strains, patients seem to tolerate the probiotic without adverse events (intestinal flatus), and it reduces IBS symptoms. The consensus of physicians and parents is that the probiotic is beneficial. In this study, therapy duration for adults averaged about 40 days for all types of IBS (References 81, 82).

Monitoring of Therapy

Overall monitoring of therapy in patients with IBS is related to their quality of life. Most of the treatments discussed should be tailored to the individual patient's symptoms. Dietary changes can be made to improve symptoms, but this should be done carefully to ensure the patient continues to obtain sufficient calories for growth. It is important that the child's growth parameters, such as height and weight, be monitored to ensure proper growth. The medications to treat IBS-C and IBS-D should be used to regulate stools to one soft stool per day. Patients should be monitored for any adverse effects of increasing abdominal distension or abdominal pain. Antidepressants are the other medication that should be closely followed, especially at the initiation of therapy. Patients should be monitored for suicidal ideations at the beginning of treatment and then for improvement in anxiety or depression. Again, with all the therapies for IBS, daily function and quality of life should improve.

Conclusions

Irritable bowel syndrome in pediatric patients greatly affects quality of life, both for the patient and the family. It is associated with an increased health care and economic burden. The pathophysiology of IBS is poorly understood and likely multifactorial. Emerging theories are leading to better treatments. Finding the optimal treatment for patients with IBS can sometimes be challenging, especially given the complexity of the disease. Overall, treatment for IBS must be patient-centered and individualized to each patient's perception of pain and symptoms.

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CHAPTER 19

Fluids and Electrolytes

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Learning Objectives

1. Describe the composition of body fluids, electrolytes, and regulation of osmolality in the human body.
2. Demonstrate an understanding of fluid and electrolyte maintenance requirements in pediatrics.
3. Identify clinical signs and symptoms of the various stages of dehydration.
4. Describe clinical manifestations and medical management for hyponatremic, isonatremic, and hypernatremic dehydration in pediatrics.
5. Design an individualized treatment plan for hyponatremic, isonatremic, and hypernatremic dehydration based on specific characteristics of the patient and the degree of dehydration.

Abbreviations in This Chapter

ADH	Antidiuretic hormone
ECF	Extracellular fluid
ICF	Intracellular fluid
ORT	Oral rehydration therapy
SIADH	Syndrome of inappropriate antidiuretic hormone secretion
TBW	Total body water

Introduction

Composition of Body Fluids

In the human body, water is the largest compartment compared with the other nutritional components including protein, fat, and carbohydrate. As humans age, total body water (TBW) as a percentage of body weight slowly decreases as described in Figure 1 (see Pediatric Pharmacokinetics chapter). The fetus has the highest TBW content, which gradually decreases to about 75% for a full-term infant. During the first year of life, the TBW will decrease to about 60% and remain steady at this percentage until puberty. In general, the TBW is 60% in men and 50% in women (Reference 1). This discrepancy occurs because, during puberty, a female's fat content increases more than that of men, and men tend to have more muscle mass than women. This affects the TBW of men and women because the fat content has a lower water content, and the muscle content has a higher water content (Reference 2).

Water is distributed between two main compartments: intracellular fluid (ICF) and extracellular fluid (ECF). In the adult, the ICF is composed of two-thirds of the TBW, and the ECF is one-third of the TBW, which is further divided into three-fourths interstitial fluid and one-fourth plasma (Reference 1). The fetus's and newborn infant's ECF volume is larger than the ICF volume, but it decreases with age. By 1 year of age, the ratio of ECF and ICF approaches the adult level because of the postnatal diuresis at birth and the continued expansion of the ICF compartment caused by cellular growth (References 2–4). The interstitial fluid, which is about 15% of the body weight, will increase in the presence of pathologic conditions such as heart failure, liver failure, nephrotic syndrome, and hypoalbuminemia (Reference 2). The plasma is about 5% of the total body weight. It is estimated that the plasma in neonates is 85–100 mL/kg compared with 60–70 mL/kg of body weight in adolescents and adults (Reference 3). The plasma volume can be affected by different pathologic conditions including dehydration, anemia, polycythemia, heart failure, abnormal plasma osmolality, and hypoalbuminemia.

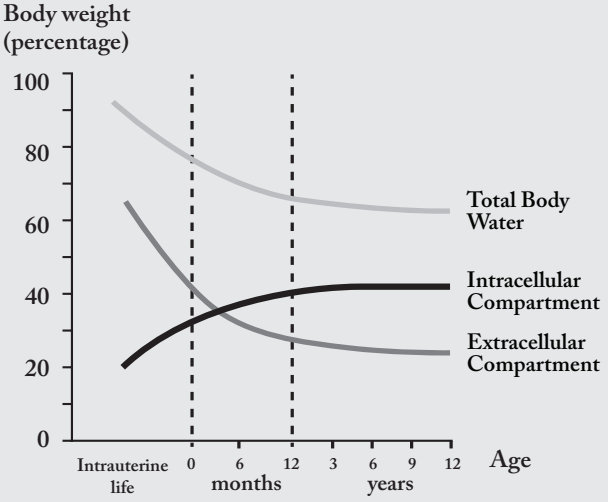


Figure 1. Total body water, intracellular fluid, and extracellular fluid as a percentage of body weight and a function of age. Used with permission from Winters RW. Water and electrolyte regulation. In: Winters RW, ed. The Body Fluids in Pediatrics. Boston: Little, Brown, 1973.

Electrolyte Composition

The composition of solutes is different in the ICF versus the ECF. In the ICF, potassium is the predominant cation, and phosphate is the predominant anion (Reference 1). The activity of the Na, K-ATPase pump (sodium pump) in plasma membranes is responsible for the low-sodium and high-potassium intracellular concentrations. In the ECF (plasma and interstitial fluid), sodium and chloride are the dominant cations and anions, respectively. Sodium excretion, which can affect the ECF volume, occurs mainly through urine, sweat, and feces. The intake and output of chloride usually parallels that of sodium, and the kidney plays a major role in regulating the reabsorption of filtered chloride. Table 1 describes the approximate electrolyte composition of ECF and ICF.

Table 1. Approximate Electrolyte Composition of the ECF and ICF

	ECF (mEq/L)	ICF (mEq/L)
Na^+	135–145	10–20
K^+	3.5–5	120–150
Cl^-	95–105	0–3
HCO_3^-	22–30	10
Phosphate	2	110–120

EFC = extracellular fluid; ICF = intracellular fluid.
Information from reference 1.

Regulation of Osmolality

Osmolality represents the number of osmoles (solutes) per kilogram (Osm/kg). The solution of higher osmolality represents more solute and less water per unit volume. However, solutions of lower osmolality have less solute and more water. Water is the primary factor in maintaining osmotic balance because it moves freely across the cell membrane between the ECF and ICF. If there is any disturbance affecting the osmolality balance between the body fluid compartments, water will respond to changes in the osmotic shifts (References 2, 3). For example, in a child with a diagnosis of diabetic ketoacidosis, the high blood glucose present in the body causes an increase in the osmolality of the ECF. This results in a shift in water from the ICF to the ECF to maintain the osmotic equilibrium.

Normal serum osmolality is about 285–295 mOsm/kg. Plasma osmolality is calculated by the following formula, where BUN is blood urea nitrogen:

$$\text{Serum osmolality: } 2\left[\text{Na}^+ + \frac{\text{glucose in mg/dL}}{18}\right] + \frac{\text{BUN in mg/dL}}{2.8}$$

Antidiuretic hormone (ADH) plays a significant role in plasma osmolality, with responses detectable with as little as a 1% change in osmolality (Reference 2). Osmoreceptors in the hypothalamus sense changes in plasma osmolality. An increase in osmolality leads to the secretion of ADH. The circulating ADH binds to V2 receptors in the collecting duct cells of the kidney, causing an insertion of water channels (aquaporins-2) into the renal collecting ducts. Thus, ADH increases the permeability of water for reabsorption, resulting in an increase in urine concentration and a decrease in water excretion. Therefore, urine osmolality acts as an important tool in assessing water homeostasis. Urine osmolality, excluding that in neonates, ranges from 50 to 1,200 mOsm/kg (Reference 1). The high value indicates maximally concentrated urine, and the low value indicates very dilute urine. In a dehydrated patient with normal kidney function, a small volume of highly concentrated urine will be produced because the body is trying to retain water; therefore, the urine osmolality has a high value.

Fluid and Electrolyte Maintenance Requirements

Maintenance fluid and electrolytes are required because of normal losses from body basal metabolism. In general, body basal metabolism is divided into two by-products, solute and heat, that are eliminated to maintain homeostasis (References 5, 6). Soluble waste by-products from metabolism are excreted in the urine, which is also known as urinary water loss (References 6, 7). Heat is described as an "insensible water loss" and is a function of basal energy expenditure (Reference 7). Examples of insensible water losses include the evaporation of water from the skin surface, the elimination of warmed water vapor from the upper respiratory tract during exhalation, and sweating.

In a 1957 study, the caloric requirements of a child were estimated to allow a determination of maintenance fluid requirements using weight alone. A comparison of energy expenditure from the basal metabolic rate and the normal activity state is described in Figure 2. The lower line defines the basal metabolic rate at various weights, and the upper line defines the estimated total expenditure with normal activity for various weights (Reference 7). The middle line expresses the calculated energy expenditure for the average hospitalized patient at bed rest. The graph shows that, compared with body weight, the metabolic rate is higher (on a calorie per kilogram basis) in the newborn period compared with adulthood. Furthermore, this shows that the metabolic rate per unit of body weight declines with increasing age. Adolescents and adults generate less heat and solute from basal metabolism than children and infants; therefore, they need less fluid and electrolytes per unit

of body weight. Likewise, children generate less heat and solute from basal metabolism than infants or neonates and therefore require less fluid and electrolytes per unit of body weight (Reference 6).

These principles dictate how fluid requirements are calculated. Several methods (surface area method, basal calorie method, Holliday-Segar method) have been proposed to correlate maintenance requirements to body weight. All three of these methods work when used appropriately; however, the Holliday-Segar method is commonly used because the formula is easy to apply and remember. The surface area method requires an equation or table to determine the patient's body surface area, as well as the patient's height and weight. The basal calorie method requires a table and information such as weight, height, age, and activity level. This method also involves the most calculations compared with the other two methods (Reference 6).

Therefore, the Holliday-Segar method is commonly used to calculate the 24-hour maintenance fluid requirements in children (Table 2). In general, infants become dehydrated faster than older patients (adolescents); infants therefore have a higher maintenance fluid requirement on a milliliter per kilogram basis. For example, an adolescent can tolerate 12–18 hours without any oral intake when preparing for a surgical procedure, but an infant requires intravenous maintenance fluids within 4–6 hours after the last feeding for a morning surgical procedure to avoid developing dehydration. It is very important to recognize the patient populations in need of maintenance fluids versus those who can tolerate an extended period without any fluids (Reference 2).

A premature neonate and a newborn are more susceptible to insensible losses than are infants. A premature neonate has about 5 times more body surface area in relation to weight (and a newborn 3 times more), resulting in a higher fluid loss (Reference 4). Moreover, it is also important to realize that extremely low-birth-weight neonates and very low-birth-weight neonates require more fluids than a term neonate or infant. For fluid intake, neonates weighing less than 1500 g require 140–190 mL/kg of body weight per day, and neonates weighing more than 1500 g require 140–160 mL/kg body weight per day (Reference 8). Once the neonate's weight reaches 3 kg, the Holliday-Segar method is preferred.

The goal of providing maintenance fluids is to prevent dehydration, electrolyte disorders, ketoacidosis, and protein degradation. Maintenance fluids typically consist of water, glucose, sodium, and potassium. Each component of maintenance fluid plays a role in replacing the fluid and electrolyte losses needed by an average individual with normal ICF and ECF volumes over a 24-hour period (Reference 5).

Maintenance water is designed to provide enough water that the kidney does not need to dilute or concentrate the urine to maintain the fluid balance in the body (Reference 2). The amount of glucose administered to the patient is only sufficient to prevent ketoacidosis and protein degradation. The electrolytes (sodium, potassium, chloride) are present in the maintenance fluid to replace normal losses from urine and stool. For most patients, a few days without any other electrolyte supplements like calcium, phosphorous, magnesium, or bicarbonate is not problematic; therefore, they are not routinely added to the maintenance fluid therapy. The

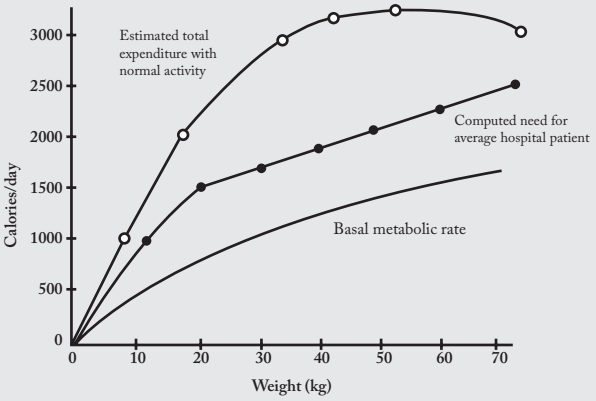


Figure 2. The comparison of energy expenditure in basal and ideal states.

Used with permission from Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics 1957;19:823–32.

Table 2. Holliday-Segar Method

Weight (kg)	24-Hour Maintenance Water Requirement for Infants, Children, and Adolescents	Maintenance Water Rate
≤ 10	100 mL/kg	4 mL/kg/hour
11–20	1,000 mL + 50 mL/kg for each kg > 10 kg	40 mL/hour + 2 mL/kg/hour × (wt – 10 kg)
> 20	1,500 mL + 20 mL/kg for each kg > 20 kg	60 mL/hour + 1 mL/kg/hour × (wt – 20 kg)

wt = weight.
Information from reference 7.

daily maintenance requirement for sodium is 2–3 mEq/kg/24 hours, potassium is 1–3 mEq/kg/24 hours, and chloride is 2 mEq/kg/24 hours in children (References 2, 9). Potassium is not required for patients with acute and chronic renal failure or in conditions in which potassium retention is present.

Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins for normal consumption in children. However, it is not problematic for a patient to receive maintenance fluids, without additional calories or nutrition, for a few days. Nevertheless, it is important to monitor the patient's weight while on maintenance fluid therapy because he or she may lose 0.5% to 1% of weight each day while on this therapy alone (Reference 2).

Intravenous fluids safe to administer parenterally on the basis of their osmolality are shown in Table 3. The solution is selected on the basis of the clinical status of the patient. In general, hypotonic fluids offer an adequate amount of water and electrolytes to match the maintenance requirements in children. The most hypotonic (lowest osmolality) intravenous solution that can be safely used is 0.45% isotonic sodium chloride (osmolality = 154 mOsm/L) (Reference 1). Any solution with an osmolality less than 154 mOsm/L is not recommended because cell lysing causes the release of potassium to the extracellular space, resulting in hyperkalemia and potentially cardiac arrhythmias and death (Reference 1). Solutions without dextrose (example: 0.45% sodium chloride solution with electrolytes) are administered to patients presenting with diabetic ketoacidosis. For patients who are taking nothing by mouth or who are pre- or post surgery, the common fluid used is 5% dextrose in 0.2% to 0.45% sodium chloride with or without potassium chloride (KCl). Neonates are a little different from children because they tend to have a difficult time excreting sodium. Therefore, fluids such as 5% or 10% dextrose in water are used to deliver isotonic fluids without an excessive sodium load while delivering the maintenance water requirements.

Dehydration

Introduction

Dehydration is a physiologic disturbance caused by the reduction or translocation of body fluids, and if severe, it can be considered a type of hypovolemic shock (Reference 10). Dehydration is one of the leading causes of morbidity and mortality in children throughout the world. Infants have the highest morbidity and mortality from dehydration because they have a larger water content, a higher metabolic turnover rate of water, renal immaturity, and an inability to independently meet their own needs. In the early process of dehydration, most of the water loss is from the ECF.

In the United States, the main cause of dehydration in children is diarrhea. Other causes of dehydration are gastroenteritis, febrile illness, stomatitis, diabetic ketoacidosis, heat prostration, and burns over 25% of the total body surface area (Reference 10). In many cases, dehydration can be managed with an oral rehydration solution, to be discussed in the following section. In more severe cases, intravenous therapy is required, especially when the patient cannot tolerate oral intake or is in hypovolemic shock (References 10–12).

Clinical Evaluation of Dehydration and Severity of Dehydration

The first step in managing a child with dehydration is to assess the severity of dehydration. Dehydration is classified as mild, moderate, and severe on the basis of the percentage of body weight loss (Table 4). This estimation is calculated as a percentage of the total amount of

Table 3. Intravenous Fluid Comparison

Solution	Osmolality (mOsm/L)	Sodium (mEq/L)	Chloride (mEq/L)	Dextrose (mOsm/L)
Lactated Ringer's solution	273	130	109	None
0.9% isotonic NaCl (normal saline)	308	154	154	None
0.45% NaCl	154	77	77	None
5% dextrose in water	252	None	None	278
5% dextrose + 0.33% NaCl	378	50	50	278
5% dextrose + 0.225% NaCl	329	38.5	38.5	278
5% dextrose + 0.45% NaCl	432	77	77	278

Information modified from reference 1.
NaCl = sodium chloride.

body weight loss based on pre-illness weight and current (illness) weight (see algorithm in Figure 3). Because infants have a higher percentage of body weight as water, the total percentages of body weight loss are higher compared with those of older children in moderate and severe dehydration (Reference 5). The history provided by the parents or caregivers is also beneficial because it may help describe the child's fluid loss and its origin (examples in Box 1) (Reference 10).

Physical Examination and Laboratory Assessment

Vital signs will help evaluate the severity of dehydration. The first vital sign change in mild dehydration is tachycardia. The respiratory rate of a patient with mild to moderate dehydration is generally normal. As the severity of dehydration worsens, the respiratory rate may increase. Severe hypotension is a sign of severe dehydration.

The skin is also a reliable organ to assess for signs of peripheral perfusion. Assessment of skin temperature, turgor, and capillary refill is useful in dehydration. For example, cool peripheral extremities are an early sign of poor perfusion, meaning there is inadequate blood flow to the peripheral part of the body. Skin turgor is measured by pinching the skin into folds (tenting) and then promptly releasing it. If there is a delay in the return of skin to its original state, then there is a decrease in skin elasticity caused by water loss. Capillary refill time is defined as the amount of time needed for vascular reperfusion after blanching pressure is applied to the nail bed (References 13, 14). If there is a delay of 2–3 seconds, moderate dehydration is indicated. However, if the capillary refill time is greater than 3 seconds, severe fluid loss and impending shock could be indicated (Reference 10).

A serum electrolyte panel may not be as helpful in predicting the degree of dehydration. Patients presenting with altered mental status, moderate to severe dehydration, or clinical signs of hypokalemia or hypernatremia or infants younger than 6 months warrant obtaining an electrolyte panel (References 12, 15). The serum sodium concentration determines the type of dehydration: hypernatremic dehydration, isonatremic dehydration, or hyponatremic dehydration. The measurement of blood urea nitrogen (BUN) or serum urea concentration is usually a marker of prerenal uremia and dehydration. Studies have shown a trend for urea concentration to increase with the degree of dehydration (References 16–20). Normally, the BUN/serum creatinine ratio is 10:15 to 1; therefore, an elevated BUN/serum creatinine ratio may imply that the patient is dehydrated.

Management of Dehydration

The severity of dehydration dictates the urgency of the situation (e.g., whether oral or intravenous therapy is required) and the volume of fluid needed to replace the loss. For a patient who can tolerate oral intake, oral rehydration therapy (ORT) is recommended.

Table 4. Signs and Symptoms Related to Severity of Dehydration

	Mild	**Moderate**	**Severe**
Infants **Older Children**	**1% to 5%[a]** **1% to 3%[a]**	**6% to 9%[a]** **4% to 6%[a]**	**> 10% (≥ 15% = shock)[a]** **> 6% (≥ 9% = shock)[a]**
Pulse	Normal, increased	Tachycardia	Rapid and weak pulse
Systolic blood pressure	Normal	Normal, low	Decreased, very low
Urine output	Decreased	Little or low UOP < 1 mL/kg/hour	Oliguria << 1 mL/kg/hour
Buccal mucosa	Slightly dry	Dry	Parched
Ant fontanelle	Normal	Sunken	Very sunken
Eyes	Normal	Sunken	Very sunken
Skin turgor/capillary refill	Normal	Delayed Cool and pale	Very delayed Cool and mottled
Skin (infants < 12 months of age)	Normal	Cool	Acrocyanosis
Tears	Normal	Decreased	No tears
Mental status	Normal	Normal to listless	Normal to lethargic or comatose
Thirst	Drinks normally; might refuse liquids	Thirsty; eager to drink	Drinks poorly; unable to drink

[a]The percentage is the amount of body weight loss based on the pre-illness weight and the current (illness) weight.
UOP = urinary output.
Information modified from references 1, 2, 12, 15.

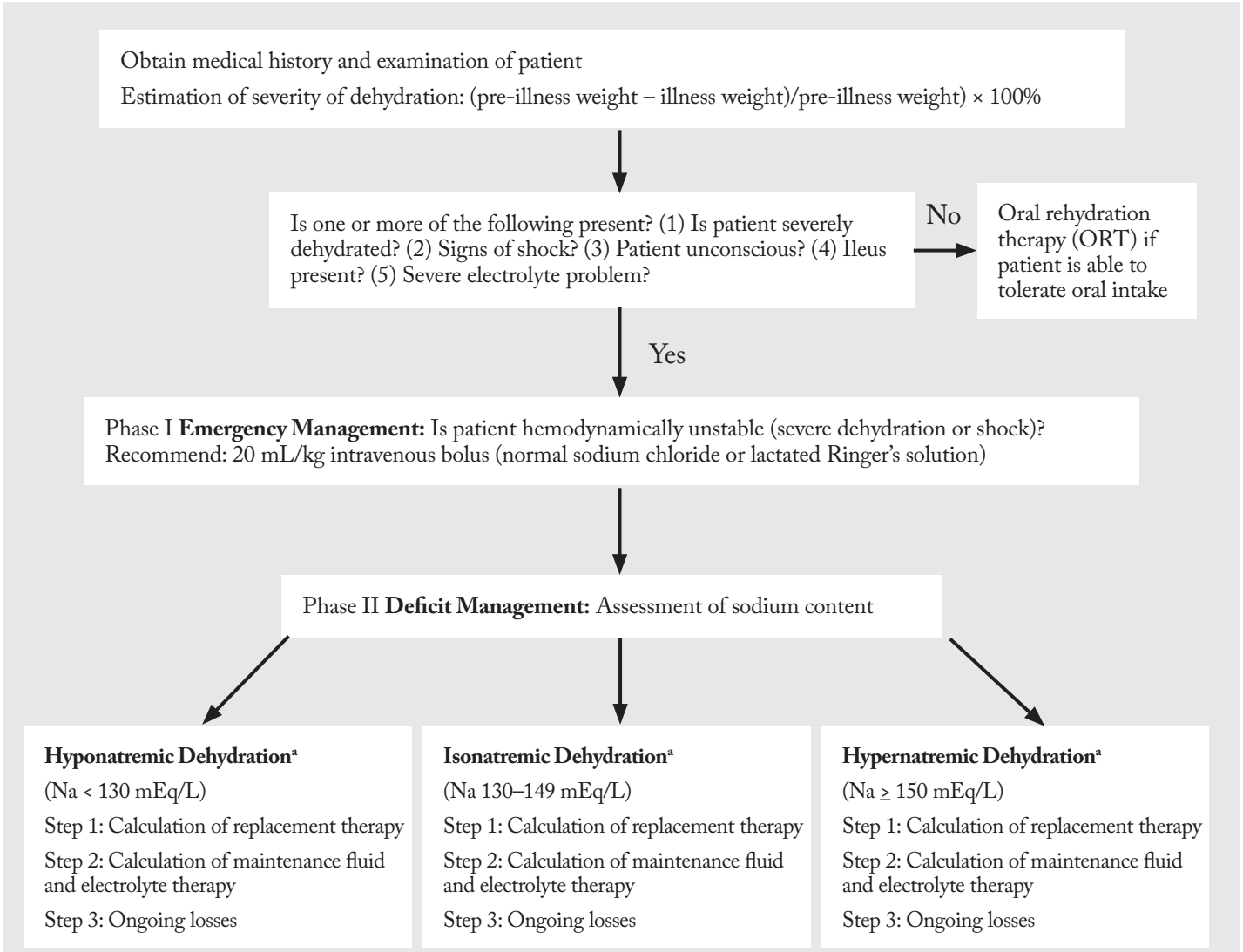


Figure 3. Algorithm for treatment of dehydration. [a]Refer to Table 6 for calculation of replacement and maintenance fluid and electrolyte therapy.

Information modified from references 9, 15.

Oral Rehydration Therapy

Oral rehydration therapy is the preferred treatment of fluid and electrolyte losses caused by diarrhea in children with mild and moderate dehydration. Several studies have shown the safety and efficacy of ORT. In addition, ORT has several potential advantages over intravenous therapy. Oral replacement therapy is less expensive, more convenient, and less traumatic to the child, and it can be given in a variety of settings such as in a physician's office, in an emergency department, or at home. The ORT solutions have successfully rehydrated more than 90% of dehydrated children and have lower complication rates than intravenous therapy (References 21, 22). In studies comparing ORT with intravenous therapy, the frequency of stools, duration of diarrhea, and rate of weight gain are similar (References 15, 22–30).

All the commercially available rehydration fluids (e.g., Pedialyte) are acceptable for ORT. They contain 2–3 g/dL of glucose; 45–90 mEq/L sodium; 30 mEq/L lactate, citrate, or acetate; and 20–25 mEq/L of potassium (Reference 9). The list of commonly used oral rehydration fluids and their composition can be found in the Constipation and Diarrhea chapter. Rehydration with solutions such as apple juice, ginger ale, sodas, sports drinks, milk, and chicken broth is discouraged because they contain low electrolyte concentrations and high carbohydrate content, and they are hypertonic (osmolality ranges from 260 to 700 mOsm/L) (References 15, 29). The high carbohydrate content may worsen diarrhea. In addition, the sodium content is generally too low, which is an important electrolyte that is lost during diarrhea and vomiting.

Box 1. Examples of information obtained from parent or caregiver.

Volume, type, and frequency of the fluid intake
Amount of urine output
Frequency of stool output and stool consistency
Frequency and volume of emesis
Recent sick contact with ill people, especially those with gastroenteritis
Use of day care
Appetite pattern
Weight loss
Recent travel history
Absence or presence of tears
Recent antibiotics use
Possible ingestions
Underlying illnesses (e.g., cystic fibrosis, diabetes, hyperthyroidism, renal disease)
Presence of fever
Presence of sweating
Hyperventilation
Changes in diet[a]
Infant formula

Information modified from reference 10.
[a]Diluted juices or water can be associated with hyponatremic dehydration, and excess salt intake or low liquid intake can be associated with hypernatremic dehydration.

Correction of mild dehydration includes giving 50 mL of ORT per kilogram plus replacement of any continuing losses during a 4-hour period. The continuing losses from stools and emesis can be accomplished by giving 10 mL of ORT per kilogram for every stool or emesis. The patient is evaluated every 2 hours for his or her progress with ORT and his or her hydration status. As soon as the patient is rehydrated, breastfeeding, formula, milk, or other recommended foods should be resumed, as should continued replacement of ongoing losses with an appropriate ORT solution (Reference 15).

For moderate dehydration, it is recommended to administer 100 mL of ORT per kilogram and to replace continuing losses during a 4-hour period. The hydration status of the patient is assessed on an hourly basis and is best accomplished in a supervised setting such as the emergency department, urgent care facility, or physician's office. Once rehydration is completed, feeding should be resumed as previously described. Controversy still lies in determining which foods are best for refeeding children. Certain foods, including complex carbohydrates (rice, wheat, potatoes, bread, and cereals), lean meats, yogurt, fruits, and vegetables, have been shown to be better tolerated in children (Reference 15).

Intravenous Therapy

The management of moderate to severe dehydration in children requires acute intervention to ensure adequate tissue perfusion. The care plan for correcting a child's dehydration requires monitoring the patient's clinical status such as vital signs during treatment, modifying the therapy as needed given the clinical situation, and assessing the electrolytes often. All children who are severely dehydrated and in a state of shock or near shock, as well as those who have severe electrolyte abnormalities, require intravenous fluid therapy. Children who are moderately dehydrated and unable to retain oral liquids because of persistent vomiting should receive intravenous therapy. In addition, intravenous therapy should be given to children who are unconscious, have an ileus, or have severe electrolyte abnormalities (References 9, 15).

Intravenous replacement therapy is generally divided into two phases: phase I emergency management and phase II deficit management, which includes a combination of deficit replacement, maintenance therapy, and ongoing losses. The overall goals of therapy are (1) restoration of skin turgor and weight, (2) recovery of alertness, (3) tolerance of oral intake of food, and (4) correction of serum chemistry levels (Reference 5). Figure 3 provides an algorithm for the treatment of dehydration. The serum sodium concentration determines the type of dehydration: hypernatremic dehydration (serum sodium 150 mEq/L or greater), isonatremic dehydration (serum sodium between 130 mEq/L and 149 mEq/L), and hyponatremic dehydration (serum sodium less than 130 mEq/L).

Phase I – Emergency Management

Volume depletion reduces the blood volume needed to adequately perfuse tissues. If not treated in a timely manner, organ damage may occur. With persistent hypovolemia, shock and death may result. For a hemodynamically unstable patient (severe dehydration or shock), one or more boluses of intravenous fluids are recommended. A common recommendation is to give 20 mL/kg of 0.9% sodium chloride or lactated Ringer's solution in the first 30 minutes. If the patient continues to be unstable after a few boluses, 40 mL/kg may be required as a bolus (Reference 9). The main goals for the correction phase are to ensure a return of adequate intravascular volume and to avoid tissue damage.

Phase II – Deficit Management

Intravenous rehydration therapy is indicated for phase II deficit management. Selecting the appropriate intravenous therapy (focusing on the sodium content of the fluid) depends on the patient's serum sodium. Patients may present with hyponatremia, isonatremia, or hypernatremia. Steps for calculating the deficit replacement

therapy and maintenance therapy of fluids and electrolytes are outlined in the discussion of specific types of dehydration (refer to the following sections of the chapter). In general, deficit replacement therapy replaces any current existing water and electrolyte deficits (i.e., sodium and water deficits). The calculated maintenance therapy volume also accounts for expected ongoing losses of water and electrolytes from a normal physiologic process.

Replacement therapy is also designed to replace any abnormal ongoing fluid and electrolyte losses. Measuring or estimating the electrolyte content of these losses and replacing them is preferred. Examples of measured losses include continued diarrhea or vomiting and aspirates from a nasogastric tube attached to suction. Other examples of estimated losses from various body fluids include gastric, pancreatic, small bowel, and bile fluids. The electrolyte composition of various body fluids is listed in Table 5 (Reference 6). Table 6 details the calculations necessary to determine the amount and type of fluids in the treatment of moderate to severe dehydration.

Table 5. Electrolyte Composition of Various Body Fluids

Fluid	Sodium (mEq/L)	Potassium (mEq/L)	Chloride (mEq/L)
Gastric	20–80	5–20	100–150
Pancreatic	120–140	5–15	90–120
Small bowel	100–140	5–15	90–130
Bile	120–140	5–15	80–120
Ileostomy	45–135	3–15	20–115
Diarrhea	10–90	10–80	10–110
Burns	140	5	110
Sweat	10–30	3–10	10–35

Information modified from references 9, 31.

Disorders of Sodium Homeostasis

Hyponatremia

Hyponatremia is defined as a serum sodium concentration less than 130 mEq/L. The pathogenesis of hyponatremia is usually a combination of sodium loss and water retention to compensate for volume depletion. The body's primary defense against developing hyponatremia is the kidney's ability to dilute the urine and excrete free water (Reference 6). It is important to determine the patient's volume status: euvolemia, hypovolemia, or hypervolemia. This will help distinguish between hyponatremia caused by low sodium and hyponatremia caused by an increase in TBW, resulting in a relative dilution of the ECF compartment (Reference 31). Hyponatremia can also be linked to renal or nonrenal causes. If the kidney is working properly, normal renal retention of sodium occurs. Thus, the urinary sodium concentration will be low (less than 10 mEq/L). However, if the kidney is the cause of sodium loss, the urine will have a sodium concentration greater than 20 mEq/L. This reflects a defect in renal sodium retention by the kidney to maintain normal homeostasis. Therefore, assessing the renal function of the patient also may play a role in the management of hyponatremia (Reference 2). Causes of hyponatremia in children are listed in Table 7.

Hypovolemic hyponatremia usually occurs in three clinical situations: a net loss of sodium in excess of water, inadequate sodium intake, and movement of sodium into cells (Reference 31). Two common causes of hypovolemic hyponatremia are acute gastroenteritis and administration of loop diuretics (furosemide, bumetanide). Patients with acute gastroenteritis experience diarrhea, which may lead to intravascular volume depletion. To compensate for the loss of water, ADH and arginine vasopressin are released. Antidiuretic hormone enhances water reabsorption in the proximal tubule, resulting in renal water retention in the collecting duct. Arginine vasopressin acts on the kidney through the V2 receptors, which leads to the reabsorption of water by the collecting ducts of the kidney, thus decreasing urine formation (Reference 1). Arginine vasopressin also binds to V1 receptors on vascular smooth muscle to cause vasoconstriction and release of prostaglandin, which results in an increase in arterial pressure. Furthermore, ADH plays a central role in thirst control, which drives the patient to consume water to replace any losses (Reference 2).

Loop diuretics (furosemide, bumetanide) cause hypovolemic hyponatremia by inhibiting the $Na^+/K^+/Cl^-$ (sodium/potassium/chloride) cotransporter of the luminal membrane in the ascending limb of the loop of Henle, resulting in a decreased reabsorption of sodium, potassium, and chloride ions. Because the use of diuretics affects the reabsorption of sodium ions, hyponatremia will result.

Euvolemic hyponatremia commonly occurs in patients with the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Common etiologies include renal, adrenal, or thyroid insufficiency, congestive heart failure, nephrotic syndrome, or medication use such as diuretics (Reference 32). In SIADH, the secretion of ADH is inhibited by neither low-sodium osmolality nor expanded intravascular volume. As a result, children with SIADH are unable to excrete water, which causes a dilution of serum sodium and hyponatremia. Retained water causes an expansion of extracellular volume, resulting in the kidney's increase in sodium excretion in an effort to decrease the intravascular volume to normal. In this clinical situation, the patient

Table 6. Treatment Summary for Dehydration

	Hyponatremic Dehydration (< 130 mEq/L)	**Isonatremic Dehydration (130–149 mEq/L)**	**Hypernatremic Dehydration (≥ 150 mEq/L)**
Step 1: Calculation of the replacement therapy			
Fluid deficit	Fluid deficit (L) = % dehydration × weight (kg)	Fluid deficit (L) = % dehydration × weight (kg)	TFD = % dehydration × weight (kg) SFD = TFD – FWD
Free water deficit[a]	Not applicable	Not applicable	FWD = 4 mL × (actual sodium – desired sodium mEq/L) × body weight (kg)
Sodium deficit[b]	Fluid deficit (L) × 0.6 (L/kg) × normal serum sodium concentration (140 mEq/L)	Fluid deficit (L) × 0.6 (L/kg) × normal serum sodium concentration (135 mEq/L)	SFD (L) × 0.6 (L/kg) × normal serum sodium concentration (140 mEq/L)
Excess sodium deficit	(Desired serum sodium [135 mEq/L] – actual serum sodium) × 0.6 (L/kg) × body weight (kg)	Not applicable	Not applicable
Potassium deficit[c]	Fluid deficit (L) × 0.4 (L/kg) × 120 mEq/L	Fluid deficit (L) × 0.4 (L/kg) × 120 mEq/L	SFD (L) × 0.4 (L/kg) × 120 mEq/L
Step 2: Calculation of maintenance fluid and electrolyte therapy			
Holliday-Segar method (Table 2)			
Step 3: Ongoing losses: Refer to Table 5 for the electrolyte composition of various body fluids.			

FWD = Free water deficit; SFD = Solute fluid deficit; TFD = Total fluid deficit.

[a]Pure water deficit is part of the TFD.
[b]0.6 L/kg means sodium distribution factor as fraction of body weight.
[c]0.4 L/kg means potassium distribution factor as fraction of body weight; 120 mEq/L is the normal value of intracellular potassium concentration.
Information from references 1,2, 9.

Table 7. Causes of Hypernatremia and Hyponatremia

Hypernatremia	**Hyponatremia**
Improperly mixed formula	Hyperglycemia
Excess sodium bicarbonate	Mannitol
Ingestion of seawater or sodium chloride	Gastrointestinal (emesis, diarrhea)
Intentional salt poisoning	Skin (sweating or burns)
Intravenous hypertonic sodium chloride	Third space losses
Hyperaldosteronism	Urinary tract obstruction and/or urinary tract infection
Nephrogenic diabetes	Thiazide or loop diuretics
Central diabetes insipidus	Cerebral salt wasting
Increased sensible losses	Diluted formula
Diarrhea	Syndrome of inappropriate antidiuretic hormone
Emesis/nasogastric suction	Hypothyroidism
Burns	Water intoxication
Excessive sweating	Nephrotic syndrome
Osmotic diuretics (e.g., mannitol)	Congestive heart failure

Information modified from reference 2.

will present in a hyponatremic state. Fluid restriction is the mainstay of therapy for SIADH. Patients should only receive between 50% and 75% of their maintenance needs (Reference 31).

Another cause of euvolemic hyponatremia in postoperative patients is the administration of maintenance fluids that are low in sodium (hypotonic fluids). When the patient is experiencing stress related to an acute illness, or surgical procedures or trauma, the body will respond by initiating a neurohormonal cascade, maintaining and retaining free water. If the patient receives a low-sodium maintenance fluid and the body fails to maintain the free water balance, hyponatremia can result. Other factors contributing to postoperative hyponatremia include a combination of ADH release, subclinical volume depletion, pain, nausea, and stress (References 31, 32).

Hyponatremic encephalopathy is a serious complication of euvolemic hyponatremia that can result in death or permanent neurologic injury. It is estimated that more than 50% of hospitalized children with a serum sodium concentration of less than 125 mEq/L will develop hyponatremic encephalopathy. Often, this is associated with SIADH or occurs during the postoperative period. Therefore, monitoring the neurologic status of patients plays a role in preventing this complication (References 31, 32).

Finally, hypervolemic hyponatremia occurs when the net water retention exceeds the sodium retention. This clinical situation will be seen in patients with edema-forming states such as congestive heart failure, cirrhosis, and nephrotic syndrome (Reference 31).

Clinical Manifestations of Hyponatremia

Hyponatremic dehydration produces more substantial intravascular volume depletion because of the shift of water from the ECF into the ICF. The decreased content of sodium in the ECF results in decreased osmolality of ECF. Physiologically, the water will move from the ECF to the ICF to maintain osmotic equilibrium. The increase in water content within the cells will cause the cells to swell. Because the brain is a fixed space in the skull, there is an increase in intracranial pressure as the brain cells swell. This brain swelling is the main cause of the neurologic symptoms that occur with hyponatremia. Symptoms suggesting neurologic complications include anorexia, nausea, emesis, malaise, lethargy, confusion, agitation, headache, seizures, coma, and decreased reflexes. As the sodium falls below 125 mEq/L, the patient may experience nausea and malaise. If the sodium continues to fall below 120 mEq/L, the patient may also develop seizures. Seizures associated with hyponatremia are more refractory to treatment with an antiepileptic and require an increase in serum osmolality to correct the underlying problem (References 1, 2).

Correction of Hyponatremia

The approach to treating hyponatremia in children involves identifying the underlying cause of hyponatremia and administering oral or intravenous therapy to correct the dehydration and hyponatremia. For mild to moderate dehydration, ORT may be used unless the child has persistent vomiting (Reference 1). If intravenous therapy is required, it is very important to avoid rapid correction of hyponatremia in children. Rapid correction of hyponatremia may cause central pontine myelinolysis, an irreversible neurologic injury. Classic features of central pontine myelinolysis include mutism, dysarthria, spastic quadriplegia, pseudobulbar, and ataxia (References 32, 33). The general recommendation is to avoid correcting the serum sodium concentration by more than 12 mEq/L during the course of 24 hours. The cornerstone of therapy is to replace the sodium and water deficits by applying the formula list included in Table 6. An aggressive initial correction is indicated for the first 3–4 hours of management, with a goal not to exceed a rise in serum sodium of 2 mEq/L per hour. The chemistry panel should be evaluated every 6 hours to determine the progress of sodium and water correction. Intravenous hypertonic sodium chloride (3% hypertonic sodium chloride solution) may be used to rapidly increase the serum sodium in children with active symptoms (e.g., seizures). Hypertonic sodium chloride solution affects serum osmolality, which leads to a decrease in brain edema. Each 4 mL/kg of 3% sodium chloride increases the serum sodium by about 1 mEq/L (Reference 9). It is recommended that hypertonic sodium chloride solution be administered through a central line because of its high osmolarity (i.e., 1027 mOsm/L). If the solution is to be administered peripherally, it should be slowly infused to minimize venous irritation and avoid infiltration. Refer to example 1 for a patient case of hyponatremia dehydration.

Isonatremia (Isotonic)

Isonatremic dehydration is defined as a serum sodium concentration between 130 mEq/L and 149 mEq/L. Isonatremic dehydration occurs when the degree of water and sodium losses is equal in both ICF and ECF. This is the most common type of dehydration in children, and the treatment plan is less complicated than that involved in hyponatremic and hypernatremic dehydration (see treatment formula, listed in Table 6).

Correction of Isonatremia

In emergency phase I for a hemodynamically unstable patient, the treatment objective is to expand the ECF volume, thereby preventing circulatory collapse. Acutely, an isotonic fluid (0.9% sodium chloride or

Example 1. Hyponatremic dehydration case.

A 12-month-old male infant presents to the emergency department with the chief concern of diarrhea and cannot tolerate any oral intake. The infant has a normal blood pressure of 85/40 mm Hg.
Today's weight: 7.5 kg; pre-illness weight: 8 kg; serum sodium content: 129 mEq/L

Estimation of severity: [(pre-illness weight – illness weight)/pre-illness weight] × 100 = (8 kg – 7.5 kg/8 kg) × 100 = **6% dehydrated = moderate dehydration**

Is one or more of the following present? (1) Is patient severely dehydrated? (2) Signs of shock? (3) Patient unconscious? (4) Ileus present? (5) Severe electrolyte problem? No

Phase I Emergency Management: **No**

Phase II Deficit Management: Assessment of sodium content = patient serum sodium content: **129 mEq/L**

Step 1: Calculation of the replacement therapy

Fluid deficit (L) = % dehydration × weight (kg) = 6% × 8 kg × 1,000 mL/kg = **480 mL**

Sodium deficit = fluid deficit (L) × 0.6 × normal serum sodium concentration (140 mEq/L) = 0.48 L × 0.6 L/kg × 140 mEq/L = 40.3 mEq = **40 mEq**

Excess sodium deficit = (desired serum sodium (135) – actual serum sodium) × 0.6 (L/kg) × body weight (kg) = (135 – 129 mEq/L) × 0.6 L/kg × 8 kg = 28.8 mEq = **29 mEq**

Potassium deficit = fluid deficit (L) × 0.4 (L/kg) × 120 mEq/L = 0.48 L × 0.4 L/kg × 120 mEq/L = **23 mEq**

Step 2: Calculation of maintenance fluid and electrolyte therapy: Holliday-Segar method

Fluid requirements: 100 mL/kg/day × 8 kg = **800 mL**

Sodium requirements: 3 mEq/kg/day = **24 mEq**

Potassium requirements: 2 mEq/kg/day = **16 mEq**

Step 3: Ongoing losses if necessary

	Water	**Sodium**	**Potassium**
Deficit Maintenance **Total**	480 mL 800 mL **1280 mL**	40 mEq + 29 mEq 24 mEq **93 mEq**	23 mEq 16 mEq **39 mEq**
First 8 hours = 1/2 remaining deficit + 1/3 daily maintenance			
1/2 remaining deficit 1/3 daily maintenance Total	240 mL 267 mL 507 mL	34.5 mEq 8 mEq 42.5 mEq	11.5 mEq 5 mEq 16.5 mEq
Next 16 hours = 1/2 remaining deficit + 2/3 daily maintenance			
1/2 remaining deficit 2/3 daily maintenance Total	240 mL 533 mL 773 mL	34.5 mEq 16 mEq 50.5 mEq	11.5 mEq 11 mEq 22.5 mEq

Fluid Selection

First 8 hours = 5% dextrose + 0.45% NaCl[a] + 20 mEq/L KCl running at 63 mL/hour

Next 16 hours = 5% dextrose + 0.45% NaCl[b] + 30 mEq/L KCl running at 48 mL/hour

[a]Sodium: 77 mEq/L × 507 mL × 1L/1000 mL = 39 mEq → selection of 0.45% NaCl solution is close to goal of 42.5 mEq.

[b]Sodium: 77 mEq/L × 773 mL × 1L/1000 mL = 60 mEq → selection of 0.45% NaCl solution is close to goal of 50.5 mEq.

Example 2. Hypernatremia dehydration case.

A 12-month-old male infant presents to the emergency department with a 3-day history of being ill. After the physical examination, the baby is assessed to be severely dehydrated with a capillary refill of 4 seconds, and his skin is cool and mottled. The infant has a low blood pressure of 70/30 mm Hg.
Today's weight: 7.2 kg; pre-illness weight: 8 kg; serum sodium content: 151 mEq/L

Estimation of severity: [(pre-illness weight – illness weight)/pre-illness weight] × 100 = (8 – 7.2 kg)/8 kg × 100 = **10% dehydrated = severe dehydration**

Is one or more of the following present? (1) Is patient severely dehydrated? (2) Signs of shock? (3) Patient unconscious? (4) Ileus present? (5) Severe electrolyte problem? **Yes, patient is severely dehydrated with hypotension.**

Phase I Emergency Management
Calculation: 20 mL/kg = 20 mL × 8 kg = **160 mL of 0.9% sodium chloride therapy**

Phase II Deficit Management: Assessment of sodium content = patient serum sodium content: **151 mEq/L**

Step 1: Calculation of the replacement therapy (round with the nearest number)
Total fluid deficit (TFD) (L) = % dehydration × weight (kg) = 10% × 8 kg × 1,000 mL/kg = **800 mL**
Free water deficit (FWD) = 4 mL × (actual sodium – desired sodium mEq/L) × body weight (kg)
4 mL × (151 – 145) × 8 kg = **192 mL**
Solute fluid deficit (SFD) = TFD – FWD = 800 mL – 192 mL = 608 mL = **0.6 L**
Sodium deficit = SFD (L) × 0.6 (L/kg) × normal serum sodium concentration (140 mEq/L) = 0.6 L × 0.6 L/kg × 140 mEq/L = 50.4 mEq = **50 mEq**
Potassium deficit = SFD (L) × 0.4 (L/kg) × 120 mEq/L = 0.6 L × 0.4 L/kg × 120 mEq/L = 28.8 mEq = **29 mEq**

Step 2: Calculation of maintenance fluid and electrolyte therapy: Holliday-Segar method
Fluid requirements: 100 mL/kg/day × 8 kg = **800 mL**
Sodium requirements: 3 mEq/kg/day = **24 mEq**
Potassium requirements: 2 mEq/kg/day = **16 mEq**

Step 3: Ongoing losses if necessary

	Water	**Sodium**	**Potassium**
Deficit	800 mL + 192 mL	50 mEq	29 mEq
Maintenance	800 mL	24 mEq	16 mEq
Total	**1,792 mL**	**74 mEq**	**45 mEq**
First 8 hours = 1/2 remaining deficit + 1/3 daily maintenance			
1/2 remaining deficit	496 mL	25 mEq	14.5 mEq
1/3 daily maintenance	267 mL	8 mEq	5 mEq
Total	763 mL	33 mEq	19.5 mEq
Next 16 hours = 1/2 remaining deficit + 2/3 daily maintenance			
1/2 remaining deficit	496 mL	25 mEq	14.5 mEq
2/3 daily maintenance	533 mL	16 mEq	11 mEq
Total	1,029 mL	41 mEq	25.5 mEq

Note: The acute phase is usually excluded from the 24-hour calculations.

Fluid selection
First 8 hours = 5% dextrose + 0.225% NaCl[a] + 20 mEq/L KCl at a rate of 95 mL/hour
Next 16 hours = 5% dextrose + 0.225% NaCl[b] + 30 mEq/L KCl at a rate of 64 mL/hour

[a]Sodium: 38.5 mEq/L × 763 mL × 1L/1000 mL = 29 mEq → selection of 0.225% NaCl solution is close to goal of 33 mEq.
[b]Sodium: 38.5 mEq/L × 1029 mL × 1L/1000 mL = 39.6 mEq → selection of 0.225% NaCl solution is close to goal of 41 mEq.

lactated Ringer's solution) is given as a bolus of 20 mL/kg over 30 minutes and repeated if necessary. As previously stated, the deficit management, phase II, requires a calculation of both fluid and sodium deficit to determine the type and amount of fluids needed. In addition, maintenance fluids and ongoing losses must be included in the overall plan. In general, the treatment plan involves providing one-half of the remaining deficit plus one-third of the daily maintenance requirement during the first 8 hours, followed by the other one-half of the remaining deficit plus two-thirds of the daily maintenance during the next 16 hours. Commonly used maintenance solutions are 5% dextrose in 0.2% to 0.45% sodium chloride containing 20 mEq/L KCl. As previously mentioned, these solutions are used because they contain a combination of water, glucose, sodium, and potassium, which are the essential elements of maintenance fluid therapy. In the presence of metabolic acidosis, potassium acetate may be used instead of KCl (Reference 34). The acetate portion of potassium acetate will convert to bicarbonate in the liver and help neutralize the acidotic state.

Hypernatremia

Hypernatremic dehydration is defined as a serum sodium concentration of 150 mEq/L or greater. The body has two defense mechanisms to protect against hypernatremia: the ability to produce concentrated urine and a powerful thirst mechanism (Reference 34). When assessing hypernatremia, it is important to distinguish between hypernatremia caused by (1) excessive sodium, (2) a water deficit, or (3) a combination of water and sodium deficit (Reference 2). In children, it is most likely related to an excess of free water loss because of increased insensible losses from fever, sweating, or gastroenteritis. Causes of hypernatremia in children are listed in Table 7.

An example of the combination of water deficit and sodium deficit is an infant or child presenting with gastroenteritis and mild hypernatremia. However, most children with gastroenteritis do not develop hypernatremia because of their supplemental intake of fluids such as water, juice, or formula, which compensates for the water deficit. If a child develops hypernatremia, it is most likely related to his or her inadequate intake of water, or lack of access to water, or anorexia (Reference 2).

Excessive sodium administration (also defined as sodium gain greater than water gain) in nonhospitalized patients may stem from improperly mixed formula, consumption of baking soda, intentional salt poisoning, and ingestion of seawater.

The classic causes of hypernatremia from inadequate water administration (water deficit) are nephrogenic diabetes and central diabetes insipidus (References 2, 34, 35). Diabetes insipidus is defined as complete or partial failure of ADH secretion (central diabetes insipidus) or renal response to ADH (nephrogenic insipidus), resulting in the excretion of hypotonic urine (Reference 31). Hypernatremia will occur if patients do not have access to water or cannot drink an adequate amount of water because of neurologic impairment, emesis, or anorexia (Reference 2). Patients with central diabetes insipidus may have a history of head trauma, central nervous infections, or tumors. However, cases of nephrogenic insipidus may be congenital or acquired (Reference 31).

Clinical Manifestations of Hypernatremia

In the hypernatremic state, the ECF is hyperosmolar because of a high serum sodium content. This state promotes water movement from the ICF to the ECF to maintain the osmotic balance. Children may appear less ill because the increased intravascular volume helps maintain their blood pressure and urine output. Only when children become more symptomatic and dehydrated do they seek medical attention (Reference 2). As a result, this treatment is delayed, and these children experience increased morbidity and mortality compared with patients who present with hyponatremia. The mortality rate of hypernatremia is 15% in children.

Hypernatremia can also cause serious neurologic damage. The movement of water from the brain cells to the ECF causes brain cell shrinkage (decrease in brain volume), tearing of blood vessels within the brain (hemorrhages), or cerebral contraction (Reference 2). Seizures and coma are possible sequelae of the brain hemorrhage. Overall, brain cell volume can be decreased as much as 10% to 15% in the presence of hypernatremia (Reference 32).

Children presenting with mild hypernatremia appear less ill than do children with isotonic dehydration. Children presenting with hypernatremia may have fever, hypertonicity, and hyperreflexia. In severely ill children, cerebral bleeding may develop. For patients with excessive sodium intoxication, signs of volume overload such as pulmonary edema may be present (Reference 2). On neurologic examination, these children may have increased tone, nuchal rigidity, and brisk reflexes. Other symptoms include myoclonus, asterixis, and chorea. Tonic-clonic and absence seizures have also been described.

Correction of Hypernatremia

The objectives for correcting hypernatremia are to prevent cerebral edema, identify the underlying causes, limit further water loss, and replace the water deficit (Reference 1). It takes 48–72 hours for idiogenic osmoles in the brain to adapt to changes in the sodium concentration during the treatment plan; therefore, the free water deficit should not be replaced too rapidly. Rapid lowering of the extracellular osmolality will result in water movement from the ECF into the brain cells, causing cerebral edema. Cerebral edema may lead to

seizures, permanent neurologic damage, or death. Hypernatremic dehydration can be treated successfully, but it is difficult to manage and should be approached with caution. Therefore, the prevention of any neurologic sequelae is important to emphasize (Reference 35).

The goal of therapy in children is to slowly correct volume deficit while correcting the serum sodium concentration by no more than 12 mEq/L during the course of 24 hours. The general first step is to restore intravascular volume (e.g., administer 0.9% sodium chloride 20 mL/kg within 20–30 minutes). Lactated Ringer's solution is avoided because it is a more hypotonic solution (osmolality = 273 mOsm/L; sodium content = 130 mEq/L), which may lead to a rapid correction of the serum sodium concentration. The correction time varies depending on the initial sodium concentration. If the initial sodium concentration is 150–157 mEq/L, 158–170 mEq/L, 171–183 mEq/L, or 184–196 mEq/L, the time required for correction is 24 hours, 48 hours, 72 hours, and 84 hours, respectively (Reference 2). It is advisable to monitor the serum sodium concentration every 4–6 hours in the initial phases of sodium concentration, thus helping to ensure that the sodium level falls slowly and gradually (Reference 36). Typical fluids used for replacement include 5% dextrose in 0.45% sodium chloride or 5% dextrose in 0.2% sodium chloride (both with 20 mEq/L KCl unless contraindicated). Total volume deficit and free water deficit must be calculated to determine the correct infusion rate and the tonicity of the fluid needed (Table 6) (References 35, 36). Refer to example 2 for a patient case. As a pharmacist, you should discontinue any medications with high sodium content and avoid using fluids with high sodium content such as 0.9% sodium chloride. If such precautions are not taken, the correction time of the high initial serum sodium concentration may be affected, or the risk of the patient's developing neurologic complications may be increased.

Conclusions

The Holliday-Segar formula remains the most popular and universally accepted method for calculating the daily maintenance fluid needs of pediatric patients. Dehydration is one of the leading causes of morbidity and mortality in children throughout the world. It commonly occurs if a child loses a large amount of fluid from diarrhea or vomiting. In assessing the patient who is dehydrated, two factors play a role: (1) the degree of dehydration and (2) the type of dehydration. For mildly and moderately dehydrated children, ORT is still the mainstay of therapy unless the patient cannot tolerate oral intake, is unconscious, or is in a state of shock. In children with severe dehydration, the key point is to calculate the fluid and electrolyte needs for deficit replacement therapy, maintenance therapy, and ongoing losses. For the hemodynamically unstable patient (severe dehydration or shock), one bolus or more is the initial step to restore an adequate intravascular volume and avoid tissue damage. Depending on the type of dehydration, the correction times are important to prevent any neurologic complications. Overall, the patient must be monitored closely, and adjustment of the fluid therapy must be directed by the laboratory values from the chemistry panel, physical examination (to check whether the signs of dehydration have improved), weight, and urine output.

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CHAPTER 20

Parenteral and Enteral Nutrition

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Learning Objectives

1. Discuss methods to assess adequate nutrition and weight gain in preterm and term infants, children, and adolescents.
2. Determine whether a pediatric patient is a candidate for specialized nutrition support (enteral or parenteral nutrition [EN, PN] therapy).
3. Formulate an EN regimen for a pediatric patient given the patient's age, disease state, and clinical status.
4. Formulate a PN regimen for a pediatric patient given the patient's age, type of intravenous access, disease state, and clinical status.
5. Identify common complications associated with EN and PN in pediatric patients.

List of Abbreviations

EN	Enteral nutrition
GI	Gastrointestinal
IVFE	Intravenous fat emulsion
MCT	Medium-chain triglyceride
PN	Parenteral nutrition
PNALD	Parenteral nutrition–associated liver disease
TNA	Total nutrient admixture

Introduction

The importance of optimal nutrition across the pediatric age spectrum cannot be underestimated. Neonates and infants, particularly those who are born prematurely, and hospitalized pediatric patients are at particular risk of adverse effects from suboptimal nutrition. Pharmacists with skills in pediatric nutrition support play a key role on the health care team in ensuring that the nutritional needs of pediatric patients are met safely and effectively. This chapter reviews nutrition assessment, requirements, and indications for specialized nutrition support in pediatric patients and outlines specific details related to the optimal provision of enteral nutrition (EN) and parenteral nutrition (PN) therapy in pediatric patients.

Nutrition Assessment

Adequate growth should be routinely monitored in healthy and hospitalized infants and children by measuring weight, length or height, and head circumference. These measurements are then used to plot development on growth curves, whereby growth is expressed as an expected percentile for age (based on population standards). Several growth charts are available; the appropriate chart to use varies on the basis of age and sex, and in infants, whether the infant is human milk or formula fed (see the Introduction to Pediatrics chapter) (References 1, 2). Growth charts are used to determine whether infants and children are growing appropriately and are critical in identifying patients with failure to thrive across the pediatric age spectrum. Growth charts using body mass index are useful in identifying children and adolescents at risk of overnutrition or obesity, the prevalence of which has increased significantly during the past few decades (References 3, 4). Of note, growth percentiles may increase or decrease in infants, whereas children should generally follow their own growth curves over time. Standard growth charts can be used for preterm infants, provided corrections for gestational age are made for weight until 24 months, length until 40 months, and for head circumference until 18 months postnatal age (Reference 5). Alternatively, the Fenton growth chart may be used for preterm infants from 22 to 50 weeks' gestational age (Reference 6).

Compared with adults, pediatric patients have greater nutrient needs per kilogram and reduced reserves (Reference 7). Significant development related to nutrition occurs during the third trimester and the immediate postnatal period. The maximal period of growth and maturation of the gastrointestinal (GI) tract occurs throughout the third trimester. Nutritive sucking, necessary for oral feeding, is fully developed at 32–34 weeks' gestation. Gastric capacity is limited at birth, causing neonates to feed more frequently than older infants. Feeding issues, including gastroesophageal reflux, are common in infants and particularly preterm infants. Infants may also present with failure to thrive in which they are not gaining weight according to normal growth curves. This can be the result of inadequate intake or improper reconstitution of formula, or it can be indicative of a pathophysiologic condition such as cystic fibrosis, hypothyroidism, or pyloric stenosis.

Infants have greater total body water per weight than older children or adults, and the percentage of extracellular fluid is even greater in preterm infants. During the first few days after birth, there is contraction of the extracellular fluid and a significant diuresis that is accompanied by a decrease in weight. This weight should be regained within the first to second week of life. Weight gain velocity is greatest during the first few months of life. Term infants should gain about 20–30 g/day, leading to a doubling of their birth weight by about 4 months of age (Reference 8). Growth then slows such that infants triple their birth weight by the end of the first year of life (Reference 9). Preterm infants may grow even faster. An infant's length normally increases by 50% during the first year (Reference 8). From 2 to 10 years, children gain about 2–3 kg/year and grow 2.5–3.5 inches/year (Reference 9). Other methods of nutrition assessment in pediatric patients include anthropometric measurements (arm circumference and tricep skinfold thickness), visceral protein (albumin, transferrin, prealbumin or transthyretin, retinol-binding protein) measurement, and urine studies for nitrogen balance. With respect to visceral protein status, note that concentrations can also be influenced by other factors including hydration status, metabolic stress, organ dysfunction, and other disease states (Reference 10).

Specialized Nutrition Support

Indications

In general, specialized nutrition support, to include EN and PN, is necessary in patients who are malnourished or at risk of being malnourished (Reference 11). Enteral nutrition, or the delivery of nutrition by tube to the GI tract, is indicated in premature neonates younger than 32–34 weeks' gestation because the suck-swallow reflex has not fully developed, in infants too sick to breast- or bottle-feed, in patients who are mechanically ventilated, and in any pediatric patient whose needs cannot be met by the oral route (Reference 11). Parenteral nutrition, or the delivery of nutrition directly to the bloodstream through a peripheral or central venous catheter, is indicated in pediatric patients when nutritional needs cannot be met by EN or when the GI tract is not functioning. Common examples of indications for PN in infants include prematurity, small bowel resection resulting in short bowel syndrome, abdominal wall defects (gastroschisis and omphalocele), necrotizing enterocolitis, intestinal atresias or webs, malrotation/volvulus, Hirschsprung disease, imperforate anus, diaphragmatic hernia, tracheoesophageal fistula, and meconium aspiration. Other disease states or conditions in which PN therapy may be indicated include critical illness, trauma, extracorporeal membrane oxygenation, appendicitis, pancreatitis, chylothorax, failure to thrive, chronic malabsorption/diarrhea, organ failure, and exacerbations of inflammatory bowel disease. In patients unable to meet nutritional requirements with EN therapy, PN should be initiated within 24 hours in preterm neonates and within 5–7 days in older pediatric patients (References 11, 12).

Fluid and Caloric Requirements

When initiating EN or PN support, fluid and caloric needs should be assessed. Table 1 outlines fluid and caloric needs across the pediatric age spectrum (Reference 13). Increased fluid requirements exist with prematurity because of increased losses from evaporation through the skin, immature renal conservation, and the use of radiant warmers and phototherapy. Excess fluid provision may be detrimental with specific disease states such as bronchopulmonary dysplasia, intraventricular hemorrhage, patent ductus arteriosus, congestive heart failure, and liver or renal failure (see Fluid and Electrolytes chapter). Caloric requirements may be increased because of critical illness and disease states such as congenital heart disease or bronchopulmonary dysplasia, or they may be decreased because of developmental delay or immobility. Caloric provision should be reassessed in pediatric patients not gaining appropriate weight or gaining weight too rapidly.

Enteral Nutrition

Enteral nutrition may be provided through nasogastric, gastric, or jejunal tube. It may be given by bolus administration or by intermittent, continuous, or cyclic enteral infusion.

What to Feed

Exclusive breastfeeding is recommended by the American Academy of Pediatrics for the first 6 months of life, with support for continued breastfeeding for the first year and beyond. Expressed human milk should be given whenever possible in patients who are receiving their nutrition enterally. In addition, donor breast milk is available through the Human Milk Banking Association of North America (Reference 14). Advantages of human milk feeding include decreased upper respiratory infections (particularly otitis media), urinary tract infections, necrotizing enterocolitis, meningitis, diarrhea, sepsis, sudden infant death syndrome, diabetes, cancer, asthma, and obesity. Although there is a risk of jaundice and kernicterus because of the inhibitors of glucuronyl transferase (responsible for bilirubin conjugation) present in breast milk, this potential risk does not outweigh the benefits of human milk feeding in most patients.

Table 1. Fluid, Caloric, Macronutrient, and Electrolyte Daily Requirements Across Pediatric Ages (References 11, 13, 18, 31)

Requirement					
	< 1500 g	**1500–2000 g**	**2–10 kg**	**> 10–20 kg**	**> 20 kg**
Fluid	130–150 mL/kg	110–130 mL/kg	100 mL/kg	1000 mL + 50 mL/kg > 10 kg	1500 mL + 20 mL/kg > 20 kg
	Preterm neonate	**1–12 months**	**1–7 years**	**7–12 years**	**12–18 years**
Calories	90–120 kcal/kg	80–105 kcal/kg	75–90 kcal/kg	50–75 kcal/kg	30–60 kcal/kg
	Preterm neonate	**1–12 months**	**1–10 years**	**11–17 years**	
Protein	3–4 g/kg	2–3 g/kg	1–2 g/kg	0.8–1.5 g/kg	
Fat	1–3 g/kg	1–3 g/kg	1–3 g/kg	1–3 g/kg	

	Preterm Neonate	**Infants/Children**	**Adolescents**
Sodium	2–5 mEq/kg	2–4 mEq/kg	1–2 mEq/kg
Potassium	2–4 mEq/kg	2–4 mEq/kg	1–2 mEq/kg
Calcium	2–4 mEq/kg	0.5–4 mEq/kg	10–20 mEq
Phosphorus	1–2 mmol/kg	0.5–2 mmol/kg	10–40 mmol
Magnesium	0.3–0.5 mEq/kg	0.3–0.5 mEq/kg	10–30 mEq
Acetate/Chloride	Variable	Variable	Variable

Infant formulas are available for feeding infants whose mothers are unable to breastfeed or provide expressed human milk. Enteral formulas for administration to children are also commercially available. Formulas come as ready-to-feed products, dry powders, and concentrated liquids. Caregivers should be educated on the proper technique for formula reconstitution and storage.

Most standard infant formulas provide 20 kcal/oz (0.67 kcal/mL) of formula; however, some may be available as 22 kcal/oz (0.73 kcal/mL) and 24 kcal/oz (0.8 kcal/mL). The caloric density of a formula may be increased further by concentrating a powdered formula or using protein-, carbohydrate-, or fat-source modular additives. Standard child formulas are typically available as 30 kcal/oz (1 kcal/mL). See Table 2 for examples of standard and therapeutic preterm and term infant formulas and standard and therapeutic child formulas that are commercially available, their indications for use, and their caloric density. Figure 1 outlines examples of calculations for EN feeding regimens based on patient age, caloric goal, and caloric density of formula.

Drug-Nutrient Considerations

Patients with enteral feeding tubes often need to receive medications through the tube. However, several factors need to be considered when drugs designed for oral administration are delivered in this manner. Only certain drug formulations should be given through an enteral tube. Although some parenteral formulations have been given enterally, this practice is generally not recommended because these formulations are meant for parenteral administration. Enteric-coated and modified-release products should be avoided because they cannot be crushed. Immediate-release solid dosage forms may be given after being ground and mixed with water. Liquid formulations can also be used, but not all are appropriate for administration through a tube. Suspensions may be too viscous and require dilution, or they may have granules with modified-release properties. Additives and electrolytes in liquid formulations may also increase their osmolality.

The site of absorption and action of the drug should also be considered. Some drugs have absorption throughout the GI tract, but others have specific sites of absorption that the tube may bypass, depending on the location of the distal tip. Still other medications, such as proton pump inhibitors, may be acid labile and rendered ineffective by the lower pH of the GI tract. Finally, patients with enteral feeding tubes may have undergone bowel resection, so it is important to know the length and location of the patient's functional bowel.

To avoid interactions, medications should not be added directly to an enteral feeding formula (Reference 15). Even when the formula and medications are given separately, there is still a potential for interactions that can affect the compatibility or stability of the drug or nutrient. If the volume can be tolerated, flushing between each medication will help prevent drug interactions and occlusion of the feeding tube. Caution should be exercised when mixing several medications for administration

Table 2. Commercially Available Enteral Formulas for Infants and Children

Formula Type	Brand Name[a]	Indication	Kilocalories (per oz)
Premature Infant Formulas			
Premature	Similac Special Care Enfamil Premature	Initial formula for low-birth-weight and premature infants	20–30
Transitional premature	Similac Expert Care NeoSure Enfamil EnfaCare	Transitional formula for older premature infants or after discharge home	22
Infant Formulas			
Cow's milk–based	Good Start Enfamil Premium Infant Similac Advance Similac Organic	Healthy, term infants	20–24
Lactose-free	Enfamil Gentlease Similac Sensitive	Lactose intolerance	20
Soy protein–based	Similac Soy Isomil Enfamil ProSobee Good Start Soy Plus	Lactose intolerance or galactosemia	20
Protein hydrolysate	Similac Expert Care Alimentum Nutramigen Pregestimil	Allergy or sensitivity to cow's milk or soy protein, impaired digestion or absorption	20
Free amino acid	EleCare Nutramigen AA Neocate Infant	Allergy or sensitivity to cow's milk or soy protein, impaired digestion or absorption	20
Low-fat, high MCT	Enfaport	Chylothorax or chylous ascites	30
Low iron	Similac PM 60/40	Renal insufficiency	20
Rice starch/ cereal added	Enfamil AR Similac Sensitive for Spit-Up	Gastroesophageal reflux	20
Infant/Toddler or Children's Formulas			
Cow's milk–based	Good Start 2 Similac Go and Grow Milk-Based Enfagrow Premium PediaSure	Healthy older infants, toddlers, and children	20–30
Lactose-free	Nutren Junior Boost Kid Essentials	Lactose intolerance	30
Fiber-containing	Nutren Junior Fiber PediaSure with Fiber	Many potential indications (e.g., constipation)	30
Soy protein–based	Enfagrow Soy Good Start 2 Soy PLUS Similac Go and Grow Soy-Based	Lactose intolerance or galactosemia	20
Protein hydrolysate	Peptamen Junior Vital jr. Pepdite Junior	Allergy or sensitivity to cow's milk or soy protein, impaired digestion or absorption	30
Free amino acid	EleCare Neocate Junior Vivonex Pediatric E028 Splash	Allergy or sensitivity to cow's milk or soy protein, impaired digestion or absorption	24–30
Low-fat, high MCT	Portagen	Impaired digestion or absorption of long-chain fats, chylothorax or chylous ascites	30
High calorie	Boost Kid Essentials 1.5	Increased caloric needs	45

[a]Brand names listed are examples and not a complete list of products in each category.
MCT = medium-chain triglyceride.
Source: Abbott Nutrition at www.abbottnutrition.com; Mead Johnson at www.meadjohnson.com; Nestlé Gerber at www.nestlenutrition.com; and Nutricia at www.nutricia-na.com.

through a tube because the stability and compatibility of drugs are unknown when tablets are crushed together or liquid formulations are mixed. Complete information regarding the potential for interactions between drugs and EN formulations was recently reviewed (Reference 16). Table 3 summarizes the most important medications with respect to drug-nutrient interactions.

EN Complications

Complications associated with EN include mechanical complications (feeding tube occlusion and malposition), GI symptoms (nausea, vomiting, diarrhea, cramping, aspiration, or constipation), feeding tube site infections, tubing misconnections, and aversion to oral feeding (particularly in enterally fed infants).

Parenteral Nutrition

Parenteral nutrition is a formulation composed of dextrose, amino acids, water, minerals, electrolytes, vitamins, and trace elements that is infused intravenously into the systemic circulation. Intravenous fat emulsion (IVFE) is typically given as a separate infusion in pediatric patients. Parenteral nutrition may be given through peripheral or central venous access. When giving peripheral PN, the osmolarity of the PN solution should be limited to 900 mOsm/L or less, and care should be taken to assess the catheter site regularly for signs of infiltration. Central PN requires the placement of a central catheter (i.e., a peripherally inserted central catheter or tunneled central venous catheter). When PN is initiated in infants and children, it is typically given by continuous infusion over 24 hours. In older infants and children who will be receiving long-term PN, the PN solution may be cycled over a defined period (e.g., a 12-hour PN infusion overnight).

Formula Considerations

Parenteral nutrition solutions may be formulated as a 2-in-1 admixture, in which the dextrose and amino acid solution infuses separately from the IVFE, or as a total nutrient admixture (TNA), in which all components (dextrose, amino acids, IVFE, and additives) are provided in a single solution. The use of TNAs in pediatric patients has disadvantages, including lower calcium and phosphorous solubility, inability to use a 0.2-micron filter because of the large particle size of IVFE, and inability to visualize particulates if they exist. For these reasons, the use of TNAs is not recommended in neonates and infants (Reference 18).

Components

Protein

Protein is provided as crystalline amino acids in PN formulations. The standard commercial solutions provide essential, semi-essential, and nonessential amino acids. Pediatric-specific amino acid products (e.g., Aminosyn-PF, Premasol, TrophAmine) were designed to mimic plasma amino acid concentrations of postprandial breastfed infants. These products have lower amounts of methionine, phenylalanine, and glycine, together with supplemental taurine, glutamate, and aspartate. Pediatric-specific amino acid products also have a lower pH, which imparts greater calcium and phosphorus solubility. All amino acid solutions contain varying amounts of electrolytes that should be considered part of the patient's overall electrolyte provision from PN.

Immaturity of the transsulfuration pathway, specifically hepatic cystathionase activity, during infancy prevents optimal conversion of methionine to cysteine. Thus, cysteine becomes a conditionally essential nutrient because it is further metabolized to taurine, which is essential for retinal development, neurodevelopment, and many other critical functions. Addition of 40 mg of cysteine per gram of amino acid has been shown to further normalize plasma amino acid patterns (specifically taurine concentrations) of parenterally fed infants (Reference 19). The addition of cysteine also lowers solution pH, thus enhancing calcium and phosphorus solubility (Reference 20).

Each gram of protein provides 4 kcal when oxidized for energy; however, controversy exists regarding whether protein calories should be considered in the caloric content of the PN regimen. The argument is that if adequate energy substrate is provided as dextrose and lipids, amino acids should be used for protein synthesis only, not oxidized for energy (Reference 21).

Early initiation of protein is recommended in extremely low- and very low-birth-weight preterm neonates, starting on the first day of life, to decrease protein losses and restore positive protein balances (References 22–24). Preterm neonates have the highest protein needs per kilogram to maintain growth rates similar to what occurs in utero; this protein requirement decreases with age (Reference 25). In infants, 55% of protein intake is used for growth and 45% for maintenance. As the growth rate slows, the balance changes so that only 10% of protein is used for growth by 4 years of age (Reference 26).

Carbohydrates

Dextrose serves as the main source of energy in PN, and it is commercially available as dextrose monohydrate in concentrations ranging from 5% to 70%. Final concentrations in PN formulations normally vary from 10% (or lower initially in preterm infants) to 35%, depending on the patient's age, nutritional needs, intravenous access, and condition. For example, dextrose should be limited to 12.5% or less in patients with peripheral access (Reference 27).

Each gram of dextrose yields 3.4 kcal when oxidized. Glucose oxidation rates in infants (10–14 mg/kg/minute) are greater than in older children or adults (5 mg/kg/minute) (References 28–30). When the dextrose infusion rate

Enteral Nutrition Calculations

Calculate caloric content of formulas:
20 kcal/oz of formula (standard infant formula) = 20 kcal/30 mL = 0.67 kcal/mL
30 kcal/oz of formula (standard pediatric formula) = 30 kcal/30 mL = 1 kcal/mL

Examples of enteral feeding requirements:
- For a 3-kg infant, give 100 kcal/kg or 300 kcal.
- For a 6.5-kg infant, give 100 kcal/kg or 650 kcal.
- For a 19-kg child, give 100 kcal/kg for the first 10 kg, followed by 50 kcal/kg for the next 9 kg (i.e., for each kilogram between 10 and 20 kg): 1000 kcal + 450 kcal = 1450 kcal.

Examples of volume of formula needed and regimen to provide estimated daily caloric needs:
- For a 3-kg infant receiving standard infant formula (20 kcal/oz):
  Desired daily calories = 300 kcal
  300 kcal × 30 mL/20 kcal = 450 mL (150 mL/kg)
  - Check to make sure it is calculated correctly: 450 mL × 0.67 kcal/mL = 301.5 kcal (about 300 kcal).
    Thus, this infant requires about 2 oz (60 mL) of formula every 3 hours to approximate calorie needs.

- For a 6.5-kg infant receiving standard infant formula (20 kcal/oz):
  Desired daily calories = 650 kcal
  650 kcal × 30 mL/20 kcal = 975 mL (150 mL/kg)
  - Check to make sure it is calculated correctly: 975 mL × 0.67 kcal/mL = 653 kcal (about 650 kcal).
    Thus, this infant requires about 6.5 oz (or 195 mL) of formula every 4 hours during the day (with the infant sleeping through the night – so only five feedings per day) to approximate calorie needs.

- For a 19-kg child receiving standard *pediatric* formula (30 kcal/oz or 1 kcal/mL):
  Desired daily calories = 1450 kcal = 1450 mL
  Thus, this child requires about six cans of formula (240 mL per can) per day. This can be given by mouth or by tube intermittently during the day. Alternatively, it can be given continuously at a rate of 60 mL/hour per tube, or the child can receive an increased amount (milliliters) per hour over less than 24 hours to give the patient time off the tube feeding/pumps. This calculation assumes that all caloric needs are being provided with the pediatric formula and the child is not receiving any additional calories from an oral diet.

Figure 1. Examples of enteral nutrition calculations.

is greater than the glucose oxidation rate, glycogenesis and fat deposition occur (Reference 29). Excess dextrose can lead not only to hyperglycemia, but also to hypertriglyceridemia, excess carbon dioxide production, and hepatic steatosis (Reference 29). Of note, the administration of exogenous insulin will lower the blood glucose, but it will not alter the glucose oxidative capacity.

Preterm infants are more likely to have glucose intolerance, which may result in hyperglycemia or hypertriglyceridemia. Dextrose should be advanced more slowly by about 2–3 g/kg/day in these patients. In older infants, dextrose can usually be advanced by 5 g/kg/day (References 12, 31). Other risk factors for hyperglycemia in pediatric patients include corticosteroid or catecholamine vasopressor therapy, diabetes, pancreatitis, or stress (organ failure, sepsis, or surgery) (Reference 29). Although neonates may develop significant hyperglycemia after surgery, it resolves more quickly in them, with glucose returning to preoperative levels within 12 hours postsurgery (Reference 32).

Intravenous Fat Emulsion

Intravenous fat emulsions provide a concentrated source of calories, prevent or treat essential fatty acid deficiency, and extend the life of peripheral intravenous lines. Commercially available products in the United States are soybean oil based, composed primarily of the long-chain fats, linoleic acid (omega-6 fatty acid) and linolenic acid (omega-3 fatty acid). The 20% IVFE product is preferred for use in pediatric patients because of the lower phospholipid-to-triglyceride ratio, which improves triglyceride clearance (References 18, 31, 33). The amount of linoleic acid necessary to prevent essential fatty acid deficiency can be supplied by providing 2% to 4% of the nonprotein calories, or 0.5–1 g/kg/day, from the IVFE (References 33, 34). Although 1 g of fat provides 9 kcal, the egg phospholipids that are used as emulsifying agents and the glycerol that is added to make the IVFE isotonic also provide calories, thereby

Table 3. Select Potential Drug-Nutrient Interactions with Enteral Nutrition (References 16, 17)

Drug or Class	Interaction	Recommendation
Amiodarone	An increased dose may be required when given nasoduodenally.	Administer consistently with respect to timing of enteral feeds. Monitor closely.
Carbamazepine	Adsorption to enteral tube feeds may occur.	Dilute the suspension 1:1 with water and flush after administration. Monitor closely.
Digoxin	Reduced absorption may be possible with fiber-containing enteral feeds.	Administer consistently with respect to timing of enteral feeds. Administer 1 hour before or 2 hours after feeds with high fiber or pectin. Monitor closely.
Fluoroquinolones	Reduced absorption may occur because of chelation with cations and/or interactions with the protein content in enteral feeds.	An increased dose of ciprofloxacin and levofloxacin may be needed. Hold enteral feeds 1 hour before and 2 hours after ciprofloxacin administration. Monitor closely.
Itraconazole	Reduced plasma concentrations may occur, even when separated from enteral feeds by 2 hours. An increased dose leads to increased GI adverse effects.	Do not administer with enteral feeds.
Levothyroxine	Reduced absorption may occur when not in a fasting state.	An increased dose may be needed. Monitor closely.
Phenytoin	Reduced plasma concentrations may occur.	An increased dose may be needed. Separate administration by 2 hours. Monitor closely.
Proton pump inhibitors	Denatured proteins may clog small-bore feeding tubes if diluted with juice (pantoprazole). Increased viscosity from xanthan gum may clog small-bore tubes (esomeprazole and omeprazole).	Pantoprazole is not ideal for feeding tube administration. Flush the tube well after administering esomeprazole or omeprazole.
Sevelamer	High viscosity may clog feeding tubes.	Flush feeding tube well before and after administration
Sucralfate	May complex with protein and clog feeding tubes.	Do not administer by small-bore (i.e., ≤ 12F) feeding tubes.
Warfarin	Warfarin resistance may occur because of the vitamin K content of feeds and/or binding to protein in feeds (more recent data).	Hold enteral feeds 1 hour before and after administration. Monitor the INR closely.

GI = gastrointestinal; INR = international normalized ratio.

increasing the caloric content of the 20% IVFE to 2 kcal/mL. Patients with severe allergic reactions to eggs should not receive IVFE products.

Lipid clearance is reduced in premature neonates, and rapid infusion is more likely to result in hypertriglyceridemia. Clearance is further impaired if premature neonates are receiving steroids, are stressed, or have organ dysfunction (Reference 35). Serum triglyceride monitoring is recommended when administering IVFE. A longer infusion time of 24 hours has been shown to improve IVFE tolerance and is recommended in preterm infants (References 33–35). Rapid lipid infusions have also been associated with impaired oxygenation in neonates. Soybean oil–based IVFE carry a boxed warning regarding preterm infant deaths attributed to pulmonary fat accumulation (Reference 36).

Soybean oil–based IVFE have proinflammatory effects secondary to eicosanoid production from omega-6 polyunsaturated fatty acids, and they have been thought to contribute to the development of PN-associated liver disease (PNALD). Although only soybean oil–based IVFE are available in the United States, products composed of fish oil, olive oil, medium-chain triglycerides (MCTs), and combinations of these fat sources are available in Europe. Intravenous fat emulsion products containing fish oil (with less-inflammatory omega-3 fatty acids) have been shown to improve and potentially prevent PNALD (References 37, 38).

Figure 2 gives an example of initiating a PN solution in an infant, including caloric calculations.

Electrolytes

Electrolytes added to PN solutions include sodium, potassium, calcium, phosphorus, magnesium, chloride, and acetate. Requirements vary on the basis of age, disease state, organ function, and concomitant drugs. On the basis of intravenous access, certain electrolytes should be limited. For example, potassium given through a

peripheral line should not exceed 40 mEq/L. Specifics on fluid and electrolyte management can be found in the Fluid and Electrolytes chapter. See Table 1 for typical electrolyte doses per day across pediatric ages (Reference 18). Electrolyte losses from sources other than urine, such as diarrhea or stoma output, should also be replaced.

The in utero provision of calcium and phosphorus during the third trimester approximates 120–150 mg/kg/day of elemental calcium and 70–85 mg/kg/day of elemental phosphorus (References 39–42). Supplementation of similar doses through PN is impossible without exceeding solubility limits and causing calcium phosphate precipitation. Despite the inability to supplement with similar in utero mineral doses, the highest retention of both minerals and sufficient bone mineralization has occurred in infants and children on PN when the minerals are given in a 1.7:1 calcium-to-phosphorus (milligram to milligram) ratio (References 43–45). This ratio is typically provided throughout the first year of life. Mineral requirements decrease as children age. In older children, an equimolar provision of calcium and phosphorus is optimal. It is important for severely malnourished patients to receive sufficient phosphorus to avoid the refeeding syndrome (see the Complications section for a more detailed discussion).

Acetate is provided in PN to help maintain the acid-base balance. Although bicarbonate is not compatible with PN, acetate is converted to bicarbonate in vivo. Premature neonates may be more prone to developing metabolic acidosis caused by reduced renal absorption of bicarbonate, lower pH of pediatric amino acid products, and addition of L-cysteine to pediatric amino acid–containing PN solutions. Consequently, they often need acetate added as a sodium or potassium salt.

Vitamins and Trace Elements

Vitamins are required cofactors in many metabolic processes. They include lipid-soluble vitamins (A, D, E, and K) and water-soluble vitamins (ascorbic acid and the B-complex vitamins), and both types should be provided in PN. Commercially available multivitamin products are available for use in PN solutions. Infants and young children should receive a pediatric multivitamin product, whereas children/adolescents older than 11 years should receive an adult multivitamin product. Iron is not included in commercially available multivitamin products, so it may need to be supplemented in patients on long-term PN.

Chromium, copper, zinc, manganese, and selenium are commonly added to PN solutions to prevent deficiencies. Although pediatric multitrace element products exist for use in PN solutions, they result in the underdosing of zinc in neonates and infants, who thus require additional zinc supplementation. In addition, zinc is important for immune function and wound healing, and supplemental zinc may be needed if abnormal fluid losses are occurring from wounds or increased stooling (Reference 46). Trace element contamination also occurs, primarily with chromium and manganese, in many components of PN, so they are not routinely added. Chromium, selenium, and zinc, which are eliminated renally, may accumulate in patients with renal insufficiency. Likewise, copper and manganese, which are eliminated through the biliary system, accumulate in patients with liver disease. Manganese accumulates in patients with or without liver disease who receive long-term PN, which has been associated with concerns for neurotoxicity. Although iodine supplementation is not needed in patients on short-term PN, deficiency may occur in patients receiving long-term therapy (Reference 47). Given these concerns, some pediatric practitioners individually dose trace elements rather than use the multitrace products. This practice allows the adjustment of trace elements in specific disease states or conditions or for the exclusion of trace elements, such as chromium and manganese, because of contamination.

PN Additives

Neonates have a reduced biosynthetic capacity for carnitine, a nutrient required for transporting long-chain fatty acids into the mitochondria for energy production. Because PN does not contain carnitine, neonates, particularly preterm neonates, will become deficient while receiving exclusive carnitine-free PN. Thus, carnitine supplementation in neonates expected to receive PN for more than 1 week will prevent deficiency and augment their capacity for fatty acid oxidation (Reference 48). Other pediatric patients who may benefit from carnitine supplementation include those with hypertriglyceridemia while receiving IVFE, as well as patients with short bowel syndrome, diffuse inflammatory bowel disease, or malabsorption syndromes who are receiving a portion of their calories parenterally (Reference 48).

Parenteral nutrition is not preferred as a drug vehicle because of the risk of interactions with the various components of the admixture; however, several medications can be safely added during compounding. Histamine-2 (H_2)-receptor antagonists are often used in patients who are critically ill and in those with short bowel syndrome. Ranitidine, famotidine, and cimetidine have been shown to be compatible with most PN admixtures (Reference 49). These medications should be used judiciously, however, because they have been associated with an increased incidence of necrotizing enterocolitis in infants, possibly caused by reduced inhibition of bacterial growth with higher gastric pH (Reference 50). Insulin may also be added to PN solutions to facilitate glucose metabolism, but only regular

Parenteral Nutrition Calculations

Estimate fluid and caloric needs:
For a 3-kg infant, give 300 mL/day parenterally and 300 kcal/day.

Calculate rate of infusion:
300 mL/day ÷ 24 hr/day = 12.5 mL/hr

Carbohydrate (dextrose):
Adjust dose in grams per kilogram.
Advance 2.5–3 g/kg in small, preterm infants.
Advance 5 g/kg in term infants and young children.
In general, advance by 5% per day in older children/adolescents.

Protein:
Begin with your desired protein dose on day 1 (no need to titrate up protein as you do with dextrose and fats).
Include 40 mg cysteine per gram of protein when giving pediatric amino acid products (i.e., Aminosyn PF, Premasol, TrophAmine).

Intravenous fat emulsion (IVFE):
Begin at 0.5–1 g/kg/day and advance by 0.25–1 g/kg/day until at desired daily dose.

Total calories:
Add kilocalories per day from dextrose, protein, and IVFE.
Divide total by patient weight for kilocalories per kilogram per day.

Total volume:
Add up milliliters per day from dextrose/amino acid solution and IVFE.
Divide total by patient weight for milliliters per kilogram per day.

Calculating dextrose calories:
Dextrose (g) × 3.4 kcal/g
300 mL of dextrose 10% = 300 mL × 10 g/100 mL = 30 g of dextrose × 3.4 kcal/g = 102 kcal/3 kg = 34 kcal/kg/day

Calculating protein calories:
Protein (g) × 4 kcal/g
2.5 g/kg/day × 4 kcal/g = 10 kcal/kg/day

Calculating IVFE calories:
20% fat emulsion provides 2 kcal/mL.
Need to calculate volume of fat emulsion per day:
1 g/kg/day × 3 kg = 3 g/day; 3 g ÷ 20 g/100 mL (i.e., 20% emulsion) = 15 mL; 15 mL/24 hr = 0.625 mL/hr
Round rate to 0.6 mL/hr × 24 hr/day = 14.4 mL; 14.4 mL/day × 2 kcal/mL = 28.8 kcal/day or 9.6 kcal/kg/day

Final calculations:
3-kg infant receiving PN (10% dextrose and 2.5 g/kg/day protein) at 12.5 mL/hr and 20% IVFE at 0.6 mL/hr:

Dextrose	34 kcal/kg
Amino acids	10 kcal/kg
IVFE	9.6 kcal/kg
Total	53.6 kcal/kg

Continue to advance dextrose and lipid calories to get to "goal" of 100 kcal/kg/day.

Figure 2. Examples of parenteral nutrition calculations.
hr = hour.

human insulin should be used. Modified insulin formulations should not be added. Low-dose heparin may also be added to most PN solutions to help prevent thrombosis of the catheter; however, the addition of heparin to IVFE can result in disruption of the emulsion (Reference 51). Iron dextran is the only parenteral iron formulation compatible with PN, but it is incompatible with IVFE (Reference 52).

Table 4 summarizes potential drug-nutrient interactions with commonly used PN additives.

Complications

Although PN is a lifesaving therapy for infants and children who cannot tolerate or absorb EN, it is associated with significant technical, metabolic, and infectious complications.

Technical complications may result with catheters when they are placed or later during their use. Catheters may move or be accidentally removed, or the lumen of the catheter may become occluded with a clot or biofilm. Fibrinolytic agents such as alteplase may be used to dissolve the fibrin and restore the patency of the catheter. Components of the PN solution such as calcium and phosphate may precipitate, causing an occlusion.

Although hyperglycemia and hypoglycemia may both occur, hyperglycemia is seen more often. It frequently occurs after surgery, when given with concomitant glucocorticoids, when dextrose is advanced too quickly, and in neonates. Hyperglycemia may impair the immune system and make the patient more susceptible to infectious complications (Reference 29). The most serious risk associated with hyperglycemia is the development of a hyperosmolar hyperglycemic state. Blood glucose should be monitored carefully, particularly when PN is initiated, when dextrose is advanced, or in patients who are at increased risk of hyperglycemia because of concomitant medications or their clinical condition. Hypoglycemia may occur if PN is abruptly discontinued.

Hypertriglyceridemia may occur in infants who receive excessive glucose or secondary to the inadequate clearance of IVFE. Clearance of the IVFE is improved if it is given over 24 hours. Elevated triglycerides may be the result of poor clearance of exogenous chylomicrons or caused by the mobilization of endogenous fat in response to inadequate caloric intake. Assessment of the serum sample is useful; if the IVFE is not being adequately cleared from the circulation, the serum sample will be lipemic.

Acid-base disorders are also common in patients receiving PN and may be caused by the underlying condition or, less commonly, by the PN formulation. The acetate and chloride components of PN should be adjusted to prevent or treat metabolic acid-base anomalies.

The refeeding syndrome is a potentially life-threatening complication. It is usually seen in patients who were very undernourished, causing their bodies to mobilize free fatty acids and ketone bodies for energy. If dextrose is started aggressively after a period of undernutrition, hypophosphatemia, hyperinsulinemia (or increased insulin secretion), and other electrolyte abnormalities may develop as energy metabolism is shifted to an anabolic state. Elevated insulin levels may cause fluid retention, which can result in cardiac decompensation in these patients. To prevent the refeeding syndrome, it is imperative to monitor glucose and other electrolytes in patients who were severely undernourished and to slowly advance dextrose. The risk may also be reduced in undernourished patients by providing additional phosphorus and potassium above the recommended daily allowance when PN is started (Reference 35).

Parenteral nutrition–associated liver disease, defined as a direct bilirubin equal to 2 mg/dL or more, is a common complication that may develop in 40% to 60% of children receiving long-term PN (Reference 53). In infants, PNALD normally manifests as cholestasis that can progress to liver failure and even death. In older children and adults, hepatic steatosis is more often seen. Risk factors include prematurity, sepsis, lack of enteral feeding, duration of PN, length of bowel remaining, and excessive calories (Reference 53). Components of PN have also been associated with the development of PNALD, including the amino acid composition and soybean oil–based IVFE. Fish oil–based IVFE has been shown to reverse PNALD and may help prevent the disease (References 37, 38). Other treatments include administering ursodiol, cycling PN, restricting the IVFE dose, preventing sepsis, providing trophic feeds, and preventing bacterial overgrowth with the use of antibiotics or probiotics (References 38, 53). The condition is normally reversible if EN can be advanced and PN discontinued before irreversible liver damage occurs; however, patients may require liver transplantation if the disease progresses.

Metabolic bone disease is also a multifactorial process that is more common in infants on long-term PN. It usually presents as osteopenia in preterm infants, but fractures and rickets can also occur (Reference 54). Preterm infants are at the greatest risk because they missed the third trimester when the highest calcium and phosphorus accretion normally occurs. Metabolic bone disease may be related to insufficient provision of calcium and phosphorus, increased renal excretion of calcium, or aluminum contamination in the PN solution. To reduce the incidence of metabolic bone disease in infants, calcium and phosphorus should be maximized to amounts that can be safely administered by PN, as well as given in the appropriate ratio; supplemental vitamin D may also be necessary.

Patients receiving PN therapy are at increased risk of infection because of the presence of an intravenous catheter. The most common organisms are coagulase-negative *Staphylococcus*, *Staphylococcus aureus*, *Enterococcus*, and *Candida* spp. (Reference 55). Organisms can be introduced from the skin, from the hub of the catheter, or by hematogenous spread from another location in the body. Catheter-related bloodstream infections begin with infection at the catheter site. In addition to systemic antibiotic therapy, treatment may include catheter removal. However, if the child depends on PN for hydration and nutrition, he or she will continue to require central venous access. Lock therapy may also be used in an effort to salvage the catheter (Reference 56). This may include the placement of an antibiotic or ethanol into the catheter lumen, where it is allowed to dwell for a time, after which the solution is flushed through the catheter or withdrawn. The use of antibiotic or ethanol lock therapy requires the patient to be cycled off PN and not receiving other systemic medications through the catheter for the duration of the dwell time. Thus, the dwell time can vary from a few hours per day to the entire time the catheter is not in use for PN or other medication administration. If lock therapy is being used for treatment of catheter-related bloodstream infection, it is commonly given daily, whereas lock therapy for prevention of catheter-related bloodstream infection is given less frequently (1–3 times/week). In patients with multi-lumen catheters, lock therapy should be alternated between all the lumens of the catheter for optimal results.

Safety Considerations in Nutrition Support

Specialized nutrition support has been associated with several safety issues in which serious harm and/or death have occurred. Commonly reported errors with EN that have resulted in patient death include the contamination of EN formulations and enteral feeding misconnections. Enteral nutrition contamination may occur at any point in the compounding, reconstitution, handling, and administration processes. Enteral feeding misconnections have occurred when feeding formulations for enteral delivery have been infused into non-enteral sites, such as a central venous catheter. The American Society of Parenteral and Enteral Nutrition has published EN guidelines that address these safety issues and give recommendations for preventing EN-related errors (Reference 15).

Parenteral nutrition is a complex formulation of macro- and micronutrients and additives. Parenteral nutrition has been associated with several errors that have resulted in serious patient harm and death, including calcium phosphate precipitation, contamination of PN formulation, over- or underdosing of dextrose,

Table 4. Select Potential Drug-Nutrient Interactions with PN (References 16, 20, 51, 52)

Drug or Class	Interaction	Recommendation
Albumin	Glycosylation of albumin may occur when it is exposed to dextrose. Clogging of 0.2-micron filters may occur. Creaming of TNAs may occur.	Do not add to PN formulations.
Heparin	Lipid instability may occur in the presence of high concentrations of heparin.	Add low-dose heparin to lipid-free PN formulations only.
Histamine-2 receptor antagonists	No effect on stability or effectiveness has been shown to occur.	Histamine-2 receptor antagonists may be added to PN formulations (lipid-free or TNA).
Hydrochloric acid	Cracking of TNAs may occur.	Add to lipid-free PN formulations only.
Insulin	No effect on stability or effectiveness of regular human insulin has been shown to occur. Other insulins are not compatible.	Add regular human insulin to PN formulations only.
Iron dextran	Lipid instability may occur when iron dextran is added.	Add to lipid-free PN formulations only.
Octreotide	Octreotide may be listed as physically compatible, but glycosylation may occur when it is exposed to dextrose that leads to inactive metabolites.	Do not add to PN formulations.
Sodium bicarbonate	Sodium bicarbonate combines with calcium to form a calcium carbonate precipitate.	Do not add to PN formulations.

PN = parenteral nutrition; TNA = total nutrient admixture.

omission of dextrose, iron overload, trace element overdoses, overdose of electrolytes, and heparin overdoses. Errors that have resulted in patient harm have occurred throughout the PN process (PN ordering, order entry/verification, PN compounding and labeling, and PN handling and administration). The American Society of Parenteral and Enteral Nutrition has published guidelines with recommendations for the safe provision of PN formulations (Reference 18).

Pharmacists in many different practice sites, including home care, institutional pharmacy, and clinical pharmacy, play an integral role in providing specialized nutrition support to patients. Many clinical pharmacists who specialize in nutrition support are directly responsible for ordering PN formulations. Parenteral nutrition solutions are typically compounded in the pharmacy, whereas EN formulations may or may not be dispensed from the pharmacy. Pharmacists are thus responsible for PN order review and verification before compounding. Pharmacy departments responsible for preparing EN and PN formulations should be aware of the safety issues associated with specialized nutrition support, remain current with recommended standards and guidelines for nutrition support, and institute safeguards within their practices to ensure the safe and effective administration of EN and PN to their patients.

Conclusions

Specialized nutrition support has been lifesaving for many pediatric disease states. Pharmacists practicing in nutrition support should be able to adequately assess nutrition status, understand the appropriate indications for EN and PN use in patients, order and compound EN and PN formulations, avoid drug-nutrient interactions, monitor patients for complications associated with therapy, and ensure the effective and safe use of nutrition therapy in patients.

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CHAPTER 21

Pediatric Obesity

Sandra Benavides, Pharm.D.

Learning Objectives

1. Illustrate the pathophysiology of pediatric obesity.
2. Describe risk factors associated with pediatric obesity.
3. Understand the diagnosis and classification of overweight and obesity in pediatric patients.
4. Discuss treatment goals and strategies for the management of obesity in pediatric patients.
5. List the benefits and limitations of current pharmacologic therapy for the treatment of obesity in pediatric patients.

Abbreviations in This Chapter

AAP	American Academy of Pediatrics
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
LAGB	Laparoscopic adjustable gastric band
RYGB	Roux-en-Y gastric bypass
SGA	Small for gestational age

Introduction

Pediatric obesity has reached epidemic proportions in the United States. The consequences are leading to increases in chronic health conditions that previously had only occurred in adults. Obesity can lead to many negative health outcomes in children and adolescents and substantially increases the risk of morbidity and mortality in adulthood.

Epidemiology

The prevalence of obesity in this population has been increasing since the 1960s, as illustrated in Figure 1. The most dramatic increase, however, was between the 1980s and 2000s, when obesity rates tripled in the pediatric population. The most recent estimates of obesity in children and adolescents range from 15% to 27%, as illustrated in Figure 2. Although the rates are high, they appear to have stabilized (Reference 3). Rates for specific sex, racial, and ethnic groups vary as depicted in Figure 3.

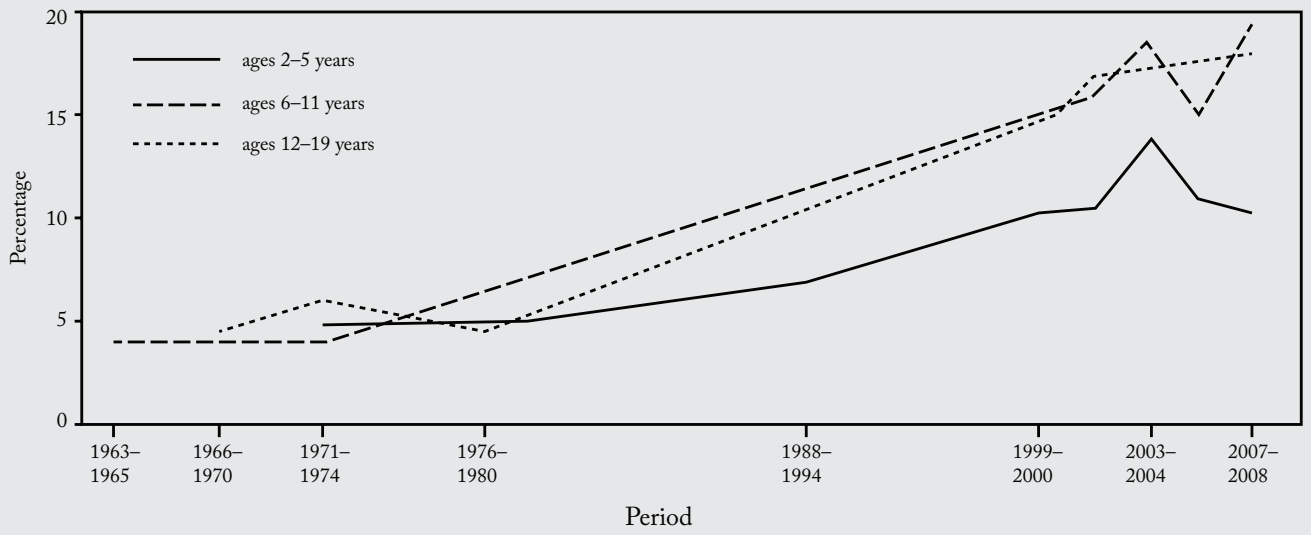


Figure 1. Rising prevalence of obesity in children and adolescents in the United States between 1963 and 2008 (Reference 1).

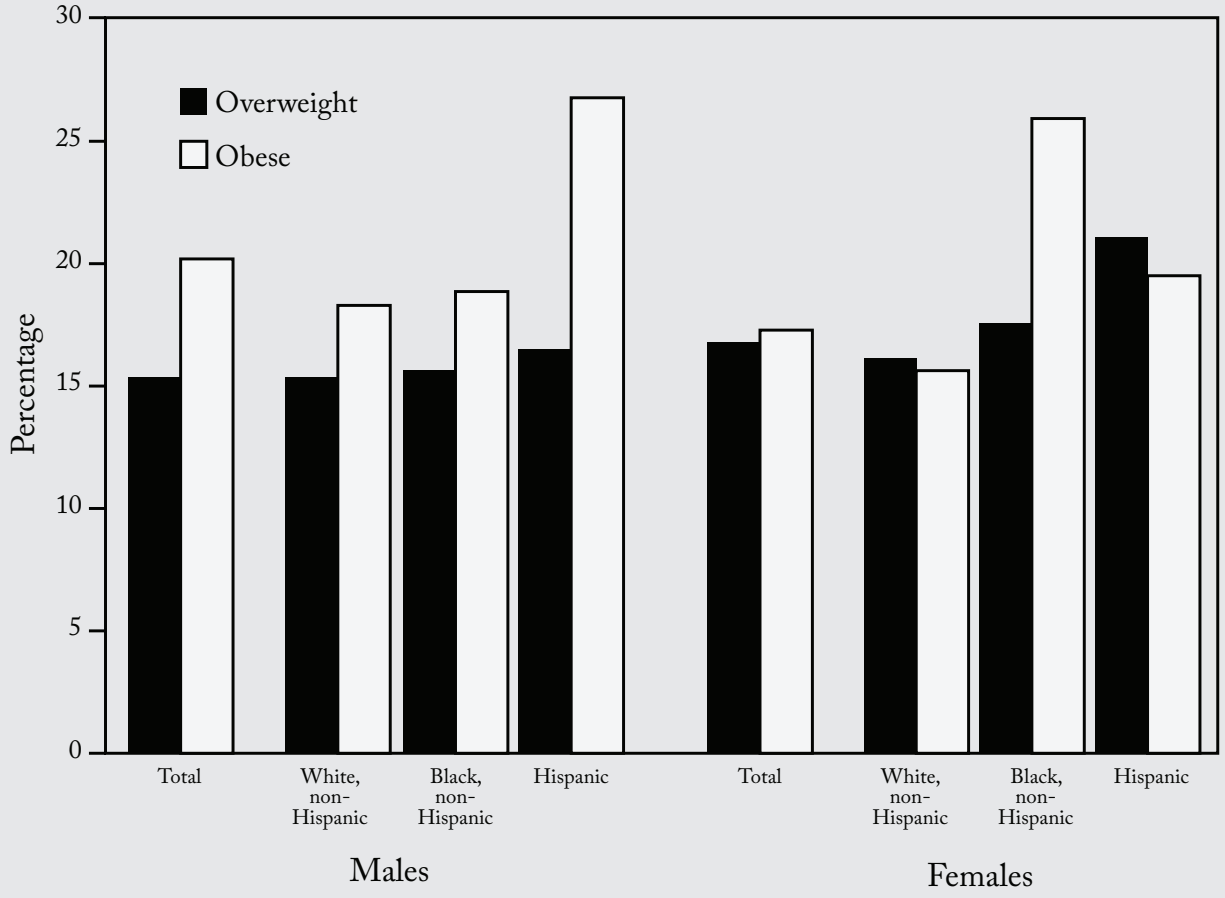


Figure 2. Prevalence of overweight and obesity in children and adolescents for 2007–2008 (Reference 2).

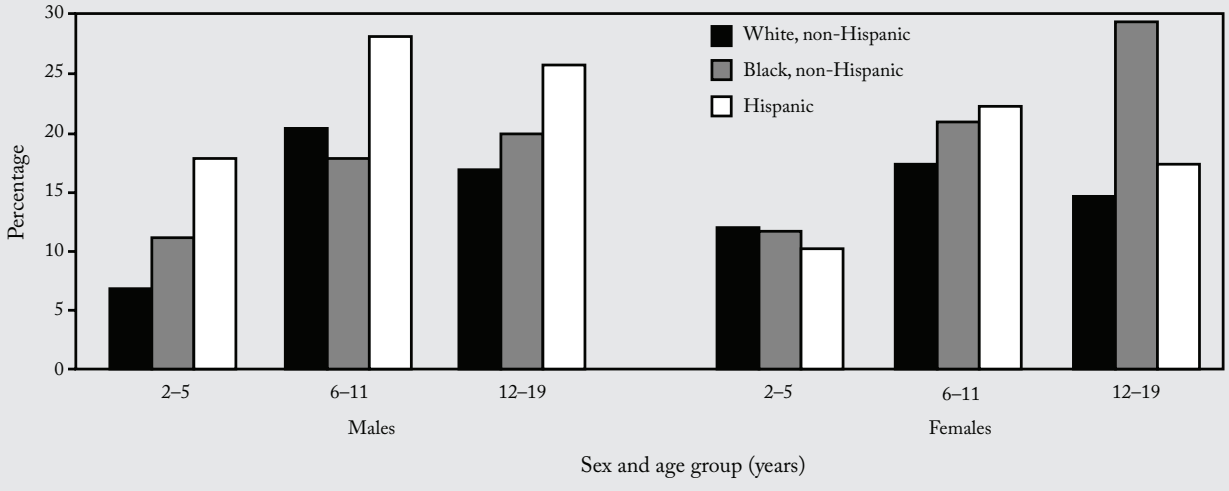


Figure 3. Prevalence of obesity among children and adolescents by sex, age group, and race/ethnicity in the United States for 2007–2008 (Reference 1).

The number of overweight children has also increased since the 1960s. More than 30% of children and adolescents between 2 and 19 years are considered overweight. Although the rates are lower for 2- to 5-year-old children at 21%, the prevalence of overweight children between 6–11 years and 12–19 years is 36% and 34%, respectively (Reference 3).

Etiology

Obesity results from a mismatch between energy consumed and energy expended. Although a genetic component may be causative in some individuals, the present epidemic of obesity is thought to be secondary to environmental factors, including increased consumption of high-caloric, energy-dense foods; decreased physical activity; and increased television and video game time.

Pathophysiology

The leptin-signaling pathway is the main biologic pathway responsible for maintaining energy balance in the body (References 4, 5). Several hormones and cytokines have been described in this pathway, as illustrated in Figure 4. Specific mutations in any part of the pathway can result in obesity. For example, deficient or low levels of leptin cause an increase in food consumption and decreased energy use, which may result in obesity. Other mutations that have been associated with obesity in children include pro-opiomelanocortin, cocaine-amphetamine–related transcript, brain-derived neurotrophic factor, and prohormone convertase 1 as well as in receptors for leptin, melanocortins, or brain-derived neurotrophic factor (Reference 4). However, these mutations account for only 3% to 4% of children and adolescents who are obese (Reference 5).

Obesity can also be a consequence of treatment of medical conditions (i.e., drug induced). Children with hypothyroidism, growth hormone deficiency, Cushing syndrome, or a history of trauma to the hypothalamus may present as overweight or obese. Syndromes associated with obesity include Prader-Willi, Bardet-Biedl, Alström, and Smith-Magenis. All of these disorders should be considered when evaluating an obese pediatric patient. Medications known to increase weight are listed in Table 1. If weight gain is identified in children or adolescents taking these medications, alternative drug therapy should be considered.

Risk Factors

Pediatric obesity has been associated with several risk factors such as intrauterine exposure to gestational diabetes, diet, decreased energy expenditure, increased television viewing, race/ethnicity, socioeconomic status, and rural residence. Critical times for the development of persistent obesity include prenatal/neonatal and early infancy, the period of adiposity rebound during the early childhood years, and adolescence.

Factors that affect obesity in childhood and adolescence during the prenatal period include maternal prepregnancy body mass index (BMI), gestational weight gain, maternal smoking while pregnant, and gestational diabetes. Infants born to mothers who are obese before pregnancy tend to be large for gestational age, have increased adipose tissue at birth, and be at increased risk of obesity in childhood and adolescence (Reference 6). As important as the mother's BMI before conception is the amount of weight gain during the pregnancy. Studies have reported that excessive weight gain during pregnancy is associated with obesity in children at age 3 years, 7 years, and in adolescence (References 7–9). Infants born to mothers with gestational diabetes are generally larger babies, have increased adipose tissue at birth, and have an increased risk of obesity and type 2 diabetes mellitus in adolescence (Reference 10).

Neonates born small for gestational age (SGA) are also at risk of subsequent obesity. The prenatal period is considered critical in "programming" the fetus's future metabolic, nutritional, and developmental status. The "programming" is based on the "thrifty phenotype" hypothesis in which the body learns to store excess fat and decrease energy expenditure when there is a perceived deficiency (Reference 11). Although these infants are born SGA, they often have rapid growth in early infancy. These infants appear to have an increased disposition for obesity, insulin resistance, and cardiovascular disease later in life (References 12, 13). Malnutrition and maternal smoking during pregnancy have been related to SGA births.

Breastfeeding is believed to have protective effects against childhood obesity. Infants who are breastfed for at least 1–3 months have a decreased risk of being obese (Reference 14). However, many of the studies that report the benefits of breastfeeding to prevent obesity are observational, and when confounding factors such as socioeconomic status and maternal BMI are considered, the benefits of breastfeeding are minimal (References 15, 16).

In infants, the BMI increases in the first year of life and peaks at around 1 year of age. After the peak, the BMI will slowly decline before it begins to increase, as depicted in the Centers for Disease Control and Prevention (CDC) BMI growth charts in Figure 5. The point at which the BMI begins to increase again is called the adiposity rebound. On average, adiposity rebound occurs in children between 5 and 7 years of age. However, if adiposity rebound occurs earlier than this (e.g., 2–3 years), the child is at an increased risk of obesity (Reference 18). Dietary factors known to increase the risk of obesity such as the overconsumption of high-calorie,

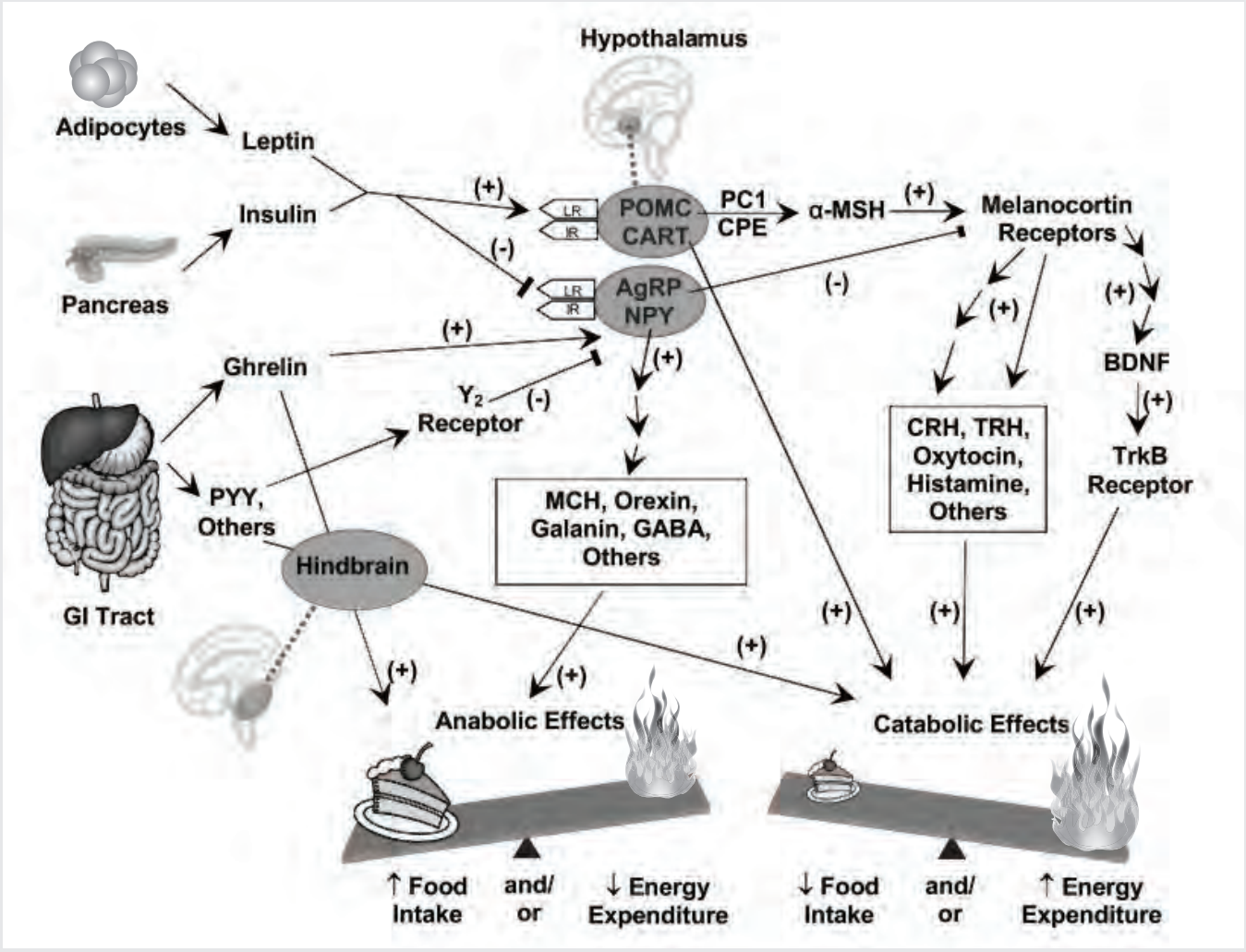


Figure 4. Leptin-signaling pathway.

AgRP = agouti-related protein; BDNF = brain-derived neurotrophic factor; CART = cocaine-amphetamine regulated transcript; CPE = carboxypeptidase E; CRH = corticotropin-releasing hormone; GABA = γ-aminobutyric acid; GI = gastrointestinal; IR = insulin receptor; LR = leptin receptor; MCH = melanin-concentrating hormone; MSH = melanocyte-stimulating hormone; NPY = neuropeptide Y; PC1 = prohormone convertase 1; POMC = pro-opiomelanocortin; PYY = peptide YY; TRH = thyrotropin-releasing hormone; TrkB = tropomyosin receptor kinase B.

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energy-dense foods and sweetened beverages may cause an early adiposity rebound (Reference 19). The overconsumption of these foods, coupled with large portion sizes at any age, also contributes to obesity in pediatrics.

Factors that have been associated with increased obesity in pediatrics are decreases in physical activity and increases in television viewing and video/computer use. Studies have shown a relationship between obesity in children and television watching and video game playing (Reference 20). As such, the American Academy of Pediatrics (AAP) recommends no television viewing or video game playing for children younger than 2 years and no more than 2 hours/day for those older than 2 years (Reference 21). The time spent on viewing/gaming may also replace the time spent on physical activity, which can further increase the risk of becoming obese. Children with sleeping problems (reported as having difficulty falling asleep and awaking several times a night between 6 months and 5 years of age) are also at an increased risk of obesity in early adulthood (Reference 22).

The most recent National Health and Nutrition Examination Survey reported that non-Hispanic white children and adolescents have an increased prevalence of obesity in relation to decreased socioeconomic status (Reference 23). However, most obese children do not live at or below poverty level. The obesity rates also decreased in the non-Hispanic white population

Table 1. Medications Associated with Weight Gain

Class	Examples
Anticonvulsants	Valproic acid, gabapentin, carbamazepine
Antihistamines	Diphenhydramine, cyproheptadine
Antihypertensive agents	Clonidine, propranolol, nifedipine
Atypical antipsychotics	Olanzapine, risperidone
Glucocorticoids	Prednisolone, prednisone
Hormonal contraceptives	Depot medroxyprogesterone
Insulin	Regular insulin, insulin aspart, glargine
Insulin secretagogues	Glyburide, glipizide
Mood stabilizers	Lithium
Tricyclic antidepressants	Amitriptyline, imipramine, nortriptyline

References 4, 5.

as the head of household level of education increased (Reference 23). With respect to race and ethnicity as risk factors for obesity, African American females and Mexican-American males appear to have had the largest increases in BMI since the 1970s (Reference 24) and the highest prevalence of obesity in the United States (Reference 3). Although urban residence is attributed to increased obesity rates worldwide, children and adolescents living in rural areas of the United States tend to be more obese compared with those living in urban areas (Reference 25).

Clinical Presentation and Diagnosis

The identification of obesity is determined on the basis of an increased amount of adipose tissue that can result in adverse health outcomes (e.g., cardiovascular disease). Although excess adipose tissue has been correlated with health risks, specifically cardiovascular disease (Reference 26), the exact amounts necessary to cause disease have not been described. In addition, there is no easy method to quantify the amount of excess adipose tissue in a pediatric patient. For that reason, weight, adjusted

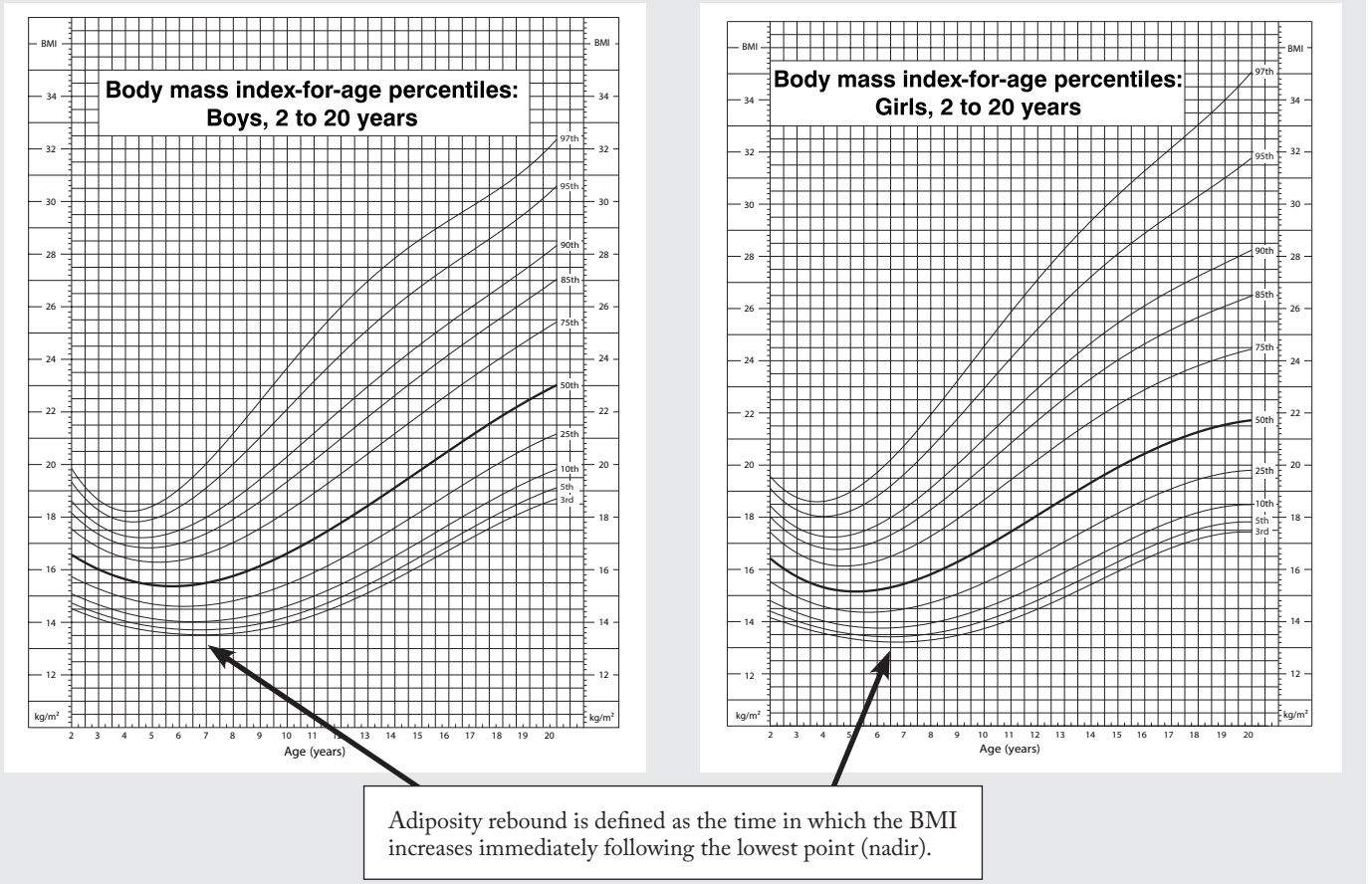


Figure 5. Centers for Disease Control and Prevention body mass index growth charts (Reference 17).

for height, is used as a measure of body fat. The accepted and recommended tool to assess body fat is the BMI, which is defined as weight (in kilograms) divided by the square of height (in meters) [BMI = kg/m^2]. In adults, specific absolute BMI values have been determined to define obesity. In pediatric patients, however, the BMI distribution changes with age, and an absolute BMI would not be appropriate to classify children as obese. For that reason, specific percentile cutoff points, as illustrated in Table 2, have been established to define obesity in children and adolescents. Of note, BMI percentiles are not available and are therefore not included in the CDC growth charts for children younger than 2 years. In this age group, infants and toddlers above the 95th percentile for weight-for-height are considered overweight, but no obesity classification exists. Because of the increase in children and adolescents who are extremely overweight, the "severe obesity" category has been established and defined as a cutoff point greater than the 99th percentile. However, the standard CDC growth charts do not designate the 99th percentile. Table 3 defines the specific cutoff points for the 99th percentile for specific ages and sex for children older than 5 years because data for children younger than 5 years are not available. The term *overweight* defines a child or adolescent who has a higher weight for height and sex, but the weight may be not be caused by excess adipose tissue. These children must be further evaluated for risk factors for future obesity.

All children and adolescents identified as either overweight or obese should be further evaluated for medical and behavioral risks of obesity and subsequent disease. Assessments should include: the child's history and physical examination, the child's growth history based on a CDC growth chart, the child's family history (including parental obesity), and the child's activity level, dietary habits, and sedentary time (Reference 27). A complete history will aid in identifying modifiable lifestyle factors. Although no specific laboratory analyses are required for diagnosing obesity, a lipid panel, fasting glucose concentration (or fasting insulin level), and baseline alanine aminotransferase and aspartate aminotransferase should be obtained (Reference 4) to assess whether complications of obesity are present. Underlying endocrine and genetic defects or syndromes must be considered when giving a child or adolescent a diagnosis of obesity.

Alternative methods of quantifying adiposity in pediatrics have been described. Direct measurement of adipose tissue using dual-energy x-ray absorptiometry, densitometry, air displacement plethysmography, or bioelectrical impedance can provide a more accurate measure of adipose tissue, but these measurements are not practical in the clinical setting. Other indirect measures of adiposity include waist circumference or skinfold measurement. Waist circumference references are available for children; however, the use of waist circumference has not been shown to increase the identification of obesity in children and adolescents over using BMI (Reference 28). Although the use of skinfold thickness helps identify obesity, the additional benefits are minimal compared with using BMI, and the measurements are more cumbersome to perform (Reference 29).

Table 2. Weight Classifications in Children and Adolescents 2–18 Years of Age

Weight Category	Criteria
Overweight	BMI-for-age between the 85th and 95th percentile
Obese	BMI-for-age greater than the 95th percentile
Severely obese	BMI-for-age greater than the 99th percentile

BMI = body mass index.
Reference 27.

Table 3. Cutoff Points for the 99th Percentile BMI for Age and Sex for Children and Adolescents Older than 5 Years

Age (years)	99th Percentile BMI Cutoff Point (kg/m^2)	
	Male	Female
5	20.1	21.5
6	21.6	23.0
7	23.6	24.6
8	25.6	26.4
9	27.6	28.2
10	29.3	29.9
11	30.7	31.5
12	31.8	33.1
13	32.6	34.6
14	33.2	36.0
15	33.6	37.5
16	33.9	39.1
17	34.4	40.8

BMI = body mass index.
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Complications

Childhood obesity has been related to increased morbidity and early mortality in adulthood (References 30, 31). In obesity, almost all body systems are affected. Table 4 lists complications associated with obesity. During the initial evaluation of an obese pediatric patient, it is important to determine the presence of any comorbidities for early intervention and treatment when necessary.

Prevention

Preventive strategies in childhood obesity begin in the prenatal period. Pregnant women should be advised to obtain adequate prenatal care, ensure proper nutrition, and stop smoking to minimize the risk of intrauterine growth restriction. In addition, although the data are limited, it is recommended to breastfeed infants for at least 6 months to potentially decrease the risk of obesity. The AAP has several obesity-preventive strategies with respect to healthy eating and physical activity (Reference 27). These strategies are listed in Figure 6.

The American Heart Association also recommends increasing fruits and vegetables to decrease the consumption of energy-dense foods (e.g., fast food, snacks). They also recommend limiting high-calorie beverages, refined carbohydrates, excess dietary fat, and large portion sizes (Reference 33). In children younger than 2 years, it is important to provide healthy meals and snacks and to limit sugar-sweetened beverages and energy-dense foods (Reference 27).

To date, no medications and/or supplements have been studied or approved for use in healthy-weight children and adolescents for the prevention of obesity.

Treatment

The treatment goal in obesity is to develop a healthy lifestyle and improve future health status (Reference 27). A recent study found that children and adolescents who are obese but lose the weight before the onset of adulthood have the same risk of type 2 diabetes mellitus, hypertension, hyperlipidemia, and atherosclerosis as children and adolescents who have never been obese (Reference 34). Such findings underscore the importance of a healthy weight in the pediatric population. However, in pediatric patients, attaining this goal may not always encompass weight loss, but rather, maintenance of growth velocity or current weight. In addition, because the stigma of being "obese" in children can cause poor self-esteem and lead to eating disorders, caution is warranted in the development of treatment plans. The AAP has detailed interventions and goals for treating obesity in children and adolescents based on age and the BMI category, as shown in Table 5.

Table 4. Complications of Obesity in Children and Adolescents

Body System	Complication
Cardiovascular	Atherosclerosis Dyslipidemia Hypertension
Central nervous system	Pseudotumor cerebri
Endocrine	Insulin resistance Polycystic ovary syndrome Pubertal advancement Type 2 diabetes mellitus
Gastrointestinal	Gallbladder disease Gastroesophageal reflux disease Nonalcoholic steatohepatitis
Mental health	Anxiety Decreased quality of life Depression Eating disorders Low self-esteem Social isolation
Orthopedic	Osteoarthritis Slipped capital femoral epiphysis
Pulmonary	Asthma Exercise intolerance Obstructive sleep apnea

References 4, 27, 32

Therapy Goals

Specific weight goals for the treatment of obesity differ on the basis of age, initial BMI category, and presence of health risks upon diagnosis, as indicated in Table 5. Because children are growing and developing, weight loss is not always a target of therapy. Goals may include weight velocity maintenance (i.e., weight gain at a stable rate), weight maintenance, slow weight gain, gradual weight loss (defined as a loss of no more than 1 lb/month), or weight loss (defined as a loss of no more than 2 lb/week). Children and adolescents who present with risks of comorbid conditions or those with a BMI above the 99th percentile have more aggressive goals. Health risks include increases in blood pressure, evidence of insulin resistance, abnormal lipid panel, and strong family history of obesity, type 2 diabetes mellitus, or cardiovascular disease. In children younger than 2 years, there is no specific weight goal regardless of the weight-for-height percentile (Reference 27).

1. Eat a well-balanced diet with regards to fat, carbohydrates, and protein as recommended by the U.S. Department of Agriculture (USDA).
2. Consume the USDA-recommended numbers of fruit and vegetables for each specific age group.
3. Eat a diet rich in calcium.
4. Eat a high fiber diet.
5. Eat breakfast every day.
6. Limit the amount of sugar-sweetened drinks including sodas, sports drinks, and sweetened fruit juice.
7. Limit the consumption of energy-dense foods.
8. Limit the number of times a family eats at restaurants, especially fast food restaurants.
9. Eat meals together as a family at the dinner table.
10. Pay particular attention to nutrition labels with regards to portion sizes in an effort to avoid large portion sizes.
11. Limit television viewing to less than 2 hours per day for children greater than 2 years of age. Children less than 2 years of age should not view any television.
12. Ensure physical activity for at least 1 hour per day.
13. Involve the entire family in healthy lifestyle modifications.

Figure 6. American Academy of Pediatrics obesity-preventive strategies (Reference 27).

Table 5. Interventions for Weight Loss and Weight Goals Based on Age and BMI Categories

Age (years)	BMI Category	Weight Goal	Initial Intervention	Highest Intervention
< 2	Weight-for-height ≥ 95th percentile	N/A	Prevention counseling	Prevention counseling
2–5	85th–94th percentile with no health risks	Weight velocity maintenance	Prevention counseling	Prevention counseling
	85th–94th percentile with health risks	Weight maintenance **OR** slow weight gain	Stage 1	Stage 2
	≥ 95th percentile	Weight maintenance **OR** Gradual weight loss (if BMI > 21 kg/m^2)	Stage 1	Stage 3
6–11	85th–94th percentile with no health risks	Weight velocity maintenance	Prevention counseling	Prevention counseling
	85th–94th percentile with health risks	Weight maintenance	Stage 1	Stage 2
	95th–99th percentile	Gradual weight loss	Stage 1	Stage 3
	> 99th percentile	Weight loss	Stage 1 (2 or 3 if family motivated)	Stage 4
12–18	85th–94th percentile with no health risks	Weight velocity maintenance; after linear growth is complete weight maintenance	Prevention counseling	Prevention counseling
	85th–94th percentile with health risks	Weight maintenance **OR** Gradual weight loss	Stage 1	Stage 2
	95th–99th percentile	Weight loss	Stage 1	Stage 4
	> 99th percentile	Weight loss	Stage 1 (2 or 3 if patient and family motivated)	Stage 4

Specific health risks include increased blood pressure, evidence of insulin resistance, dyslipidemia or strong family history of obesity, type 2 diabetes mellitus, or cardiovascular disease. Stage 1 = Prevention Plus; Stage 2 = Structured Weight Management; Stage 3 = Comprehensive Multidisciplinary Intervention; Stage 4 = Tertiary Care Intervention.
BMI = body mass index; N/A = not applicable.
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Treatment Stages

The AAP has developed five stages of intervention for the treatment of obesity in children, beginning with prevention counseling and subsequent treatment stages 1–4 (Reference 27). Prevention counseling includes the preventive strategies listed in Figure 6. Stage 1 is also known as the "Prevention Plus" stage. This stage incorporates the prevention counseling strategies with more frequent monitoring. In this treatment stage, it is recommended to allow the child to regulate his or her food intake and not to establish a "diet" or restriction of food. In implementing this stage, it is important to work with the entire family to determine goals that are reasonable for the family. For example, increasing physical activity to 1 hour/day may not be feasible, whereas starting at 15 minutes and slowly adding time may be more realistic. Also important to consider are the cultural values, financial status, work and school schedule, and motivation of the family. This stage of treatment lasts 3–6 months, and it is reevaluated if goals for the child are not being met.

Stage 2 treatment, "Structured Weight Management," incorporates many of the same healthy lifestyle strategies as stage 1, but it differs by providing more structure. In this stage, a planned diet, including daily meals and snacks, and planned physical activity are included. The meals are planned in accordance with the USDA (U.S. Department of Agriculture) Dietary Reference Intake recommendations, which limit eating and drinking (other than water) in between meal and snack time. Food intake and physical activity are monitored more closely with food recalls and logs of physical activity. The child or adolescent is monitored and reevaluated monthly in this stage of treatment and, if necessary, moves to a different treatment stage. Dietitians, physical therapists, exercise therapists, or clinicians with additional training in these areas are typically involved in the care of these patients.

Stage 3 treatment, referred to as Comprehensive Multidisciplinary Intervention, continues to follow the structure of stage 2, but it becomes more intense in both goal setting and monitoring. Diet and physical activity are set for the child or adolescent with weight loss as a goal. In this stage, a multidisciplinary approach with input from a social worker, psychologist, dietitian, exercise specialist, and physician is recommended. For optimal results, patients are initially monitored weekly for 8–12 weeks and then monthly. Commercial programs (e.g., Weight Watchers) may be suitable at this treatment stage; however, the program should be reviewed to ensure healthy strategies are used.

The highest level of treatment, Tertiary Care Intervention (stage 4), involves more intense interventions such as medications, very low-calorie diets, and weight-loss surgery. This treatment stage is reserved for those who are severely obese, those whose previous stages of treatment have failed, and those that are motivated and committed to the treatment. In addition, this stage requires the child or adolescent to have the maturity to understand the risks associated with medication and surgery. The details of medication use and surgical options for treatment will be discussed later in the chapter.

Treatment recommendations differ for children younger than 2 years. It is important to assess parental status for risk of future obesity. An infant of two obese parents is at high risk of being obese later in life, even if the infant is less than the 95th percentile in weight-for-height. It is not recommended to restrict caloric intake in this age group regardless of weight-for-height. Instead, parents should be counseled on obesity-preventive strategies. Such strategies (listed in Figure 6) include breastfeeding the infant from birth to at least 1 year of age and avoidance of sugar-sweetened beverages and high-fat, energy-dense foods (e.g., chips, French fries). For children between 12 and 24 months, additional nutritional strategies include limiting the amount of milk consumed because more than 24 oz/day may cause the child not to eat other healthy foods. At this age, it is important not to restrict food intake, but to provide the toddler with healthy meal and snack options. It is advised to provide three meals a day at a table with the family. Young children will typically eat two additional snacks per day.

Pharmacotherapy

Orlistat (Xenical) is presently the only medication approved for the treatment of obesity in the pediatric population. Previously, sibutramine (Meridia) was approved for use in adolescents older than 16 years; however, it was removed from the U.S. market in 2010 because of the increased risk of nonfatal myocardial infarctions and strokes associated with its use (Reference 35). The use of metformin (Glucophage) has shown some positive results in decreasing weight; however, it is not currently approved or recommended for use in this population. There are no nonprescription medications or supplements recommended for use in the pediatric population for the treatment of obesity.

Orlistat (Xenical)

Orlistat reversibly inhibits pancreatic lipases in the stomach and small intestine. The inhibition of the enzymes prevents the digestion of dietary fat (in the form of triglycerides) to absorbable free fatty acids and monoglycerides. As a result, orlistat inhibits around 30% of ingested dietary fat, leading to decreased caloric intake and weight loss. Orlistat is minimally absorbed as it

exerts its action in the gastrointestinal tract. It is metabolized primarily in the gastrointestinal wall, with 97% excreted in the feces. The elimination half-life of the drug is between 1 and 2 hours (Reference 36).

The efficacy of orlistat has been evaluated in pediatric patients 8–18 years of age. Clinical trials have shown a decrease in BMI ranging from 0.5 to 4.1 kg/m^2 with a dose of 120 mg three times/day (References 37–41) in combination with lifestyle modifications. About 30% of patients in clinical trials lost >5% of body weight, whereas 15% lost >10% of body weight. One study evaluating the long-term efficacy of orlistat found that the BMI decreased by 0.55 kg/m^2 in the orlistat-treated group and increased by 0.31 kg/m^2 in the placebo group after 1 year (Reference 37). However, although there was an overall decrease in BMI, participants in both treatment arms gained weight throughout the year. Clinical trials, however, had drop-out rates from 20% to 35% due to adverse drug reactions. The most commonly reported adverse drug effects included mild to moderate gastrointestinal upset in almost all the patients. These included nausea, fatty/oily stool, oily spotting, oily evacuation, fecal urgency, frequent stools, diarrhea, abdominal pain, fecal incontinence, and flatulence (with and without discharge). Other serious adverse effects reported included systemic cholelithiasis leading to a cholecystectomy in one patient (Reference 37).

Orlistat appears to decrease the absorption of fat-soluble vitamins, resulting in decreases in serum levels of vitamin D (Reference 42). All pediatric patients taking orlistat should supplement with a multivitamin containing vitamin A (5,000 IU), vitamin D (400 IU), vitamin E (300 IU), and vitamin K (25 mcg). The vitamin is best administered at least 2 hours before or after the administration of orlistat. In patients on anticoagulation therapy with warfarin, the decrease in vitamin K absorption may cause an increase in the INR (international normalized ratio). Close monitoring is warranted for patients concomitantly taking orlistat and warfarin. Orlistat also decreases the absorption of levothyroxine and cyclosporine. It is advised to separate orlistat and levothyroxine by at least 4 hours. It is not recommended to use orlistat if the patient is taking cyclosporine. However, if the two drugs are used concomitantly, they must be separated by at least 2 hours, and careful monitoring of cyclosporine levels is critical.

The recommended dose of orlistat in children older than 12 years is 120 mg orally three times/day with meals. The dose is taken during the meal or up to 1 hour after the meal. It is not recommended to exceed three doses/day. Patients should also be advised to limit fat intake to a maximum of 30% of total caloric intake and to divide between the three meals. If a meal does not contain fat, it is not necessary to take the medication. Although orlistat is available as an over-the-counter medication (Alli), the manufacturer does not recommend its use in anyone younger than 18 years.

Metformin (Glucophage)

Metformin has been evaluated for weight loss in obese children and adolescents (9–18 years of age) with and without insulin resistance. Metformin decreases hepatic glucose production and intestinal absorption of glucose and improves insulin sensitivity. On administration, about 50% to 60% is systemically absorbed. It is not bound to plasma proteins. Metformin is excreted unchanged in the urine by tubular secretion. The elimination half-life of metformin is about 17 hours (Reference 43).

Small, short-term studies of metformin for weight loss have found decreases in weight ranging from 4.4 to 6.1 kg (References 44, 45) and decreases in BMI of 0.16–0.5 kg/m^2 (References 46, 47). However, of note, these studies were short (maximum of 6 months), had a limited number of subjects, and did not always show a significant difference over placebo. Further studies are necessary to evaluate the role of metformin in weight loss of obese children and adolescents.

Commonly reported adverse effects of metformin in the studies included nausea, dizziness, and loose stools. No reports of serious adverse reactions, such as lactic acidosis, were reported. In addition, no studies monitoring serum creatinine and liver function enzymes reported any abnormalities. Minimal clinically significant drug interactions exist with metformin. However, metformin must be discontinued before administering intravenous iodinated contrast materials and not reinitiated until 48 hours after the procedure and adequate renal function is restored. Adolescents should also be cautioned regarding acute or chronic alcohol use because alcohol can increase the risk of lactic acidosis.

The doses used for weight loss ranged from 500 to 1000 mg orally twice daily. In the study using 1 g twice daily, the dose was titrated up during a 3-week period. Metformin should be given with meals.

Surgical Therapy

The last line of therapy for obesity is surgical intervention. However, before electing for weight-loss surgery in pediatric patients, the matter must be given careful consideration. Some factors to consider include BMI, comorbidities, physical and emotional maturity, and ability to adhere to the lifestyle modifications required after surgery.

In general, pediatric patients considered for weight-loss surgery include those with a BMI greater than 30 kg/m^2 with a serious comorbidity such as type 2 diabetes mellitus, moderate or severe obstructive sleep apnea,

pseudotumor cerebri, or severe steatohepatitis. Many of these comorbidities have been reported to improve or completely resolve after weight-loss surgery (References 48, 49). Other candidates for weight-loss surgery include children and adolescents with a BMI greater than 40 kg/m^2 with or without comorbidities (Reference 50).

Two types of weight-loss surgery have been successfully performed in pediatric patients: the Roux-en-Y gastric bypass (RYGB) and the laparoscopic adjustable gastric band (LAGB) procedure. The RYGB involves the creation of a 15- to 30-mL gastric pouch to bypass the small intestine (Reference 51). This form of weight-loss surgery is restrictive and decreases the amount of nutrients absorbed. In adolescents, the RYGB can lead to a weight loss of 18–22 BMI units (Reference 49) with weight loss efficacy rates reported at about 60% in adolescents (Reference 48). To date, no in-hospital deaths immediately after the surgery have been reported, although one patient with a presurgical BMI of 80 kg/m^2 died 9 months after surgery because of several complications. Complications of this surgery include shock, pulmonary embolism, severe malnutrition, postoperative bleeding, and gastrointestinal obstruction. Because the RGYB weight-loss surgery often results in nutritional deficiencies, it is recommended to postpone this surgery in children and adolescents until after they have attained at least 95% of adult stature. Two assessments should be completed before surgery, Tanner staging and evaluation of bone age (Reference 50). Because most linear growth spurts occur before puberty, it is advised to defer weight-loss surgery until after Tanner stage IV is reached in both boys and girls. In addition, bone age can be determined with radiography of the hands and feet. If this criterion is followed, the child will typically be older than 12 years. The RGYB can still be considered in individuals not meeting this criterion if they present with severe obesity and comorbidities.

The LAGB involves the placement of a silicone adjustable band on the upper portion of the stomach that results in a small pouch for food (Reference 51). The band is adjusted after surgery and throughout the weight-loss period. This form of weight-loss surgery is not restrictive and does not result in the same nutritional deficiencies as the RYGB. The LAGB has shown weight loss in adolescents ranging from 11 to 14 BMI units with weight loss efficacy rates reported from 15% to 87% (Reference 48). To date, no deaths have been reported with LAGB surgery. Complications of surgery in this population include band slippage, gastric dilation, intragastric band migration, psychological intolerance of band, hiatal hernia, cholecystitis, and cracking of the band. Currently, the LAGB is not indicated in pediatric patients and is considered investigational. Both forms of surgery still require further research to determine long-term efficacy and safety. These forms of surgery should not be considered until all other treatment options have been attempted and failed.

It is crucial for any child or adolescent being considered for weight-loss surgery to have the emotional maturity to understand the risks associated with surgery, the motivation to adhere to lifestyle modifications after the surgery, and familial support. In addition, any psychiatric condition should be actively treated and in remission for at least 1 year before the surgery is performed. Typically, the surgery is performed at a center with a multidisciplinary team specializing in obesity.

Therapy Monitoring

All children and adolescents should have a yearly height and weight assessment. In those older than 2 years, a BMI should be calculated and plotted on the CDC growth charts to determine the percentile. Any child classified as overweight or obese may require additional laboratory analysis and a physical examination for existing complications of obesity. Weight, height, and BMI are adequate assessments for follow-up; anthropometric measurements (such as skinfold and waist circumference) are unnecessary. Follow-up laboratory parameters will vary according to the individual child and his or her presenting symptoms. Dietary intake and physical activity should be reviewed at each visit.

For children and adolescents on pharmacotherapy for obesity, additional monitoring is necessary. During treatment with orlistat, a baseline vitamin D level should be obtained. Regardless of whether a multivitamin is also prescribed to the patient, a follow-up vitamin D level should be considered every 3–6 months during orlistat therapy. Patients should be monitored for adverse reactions, which typically subside within 4 weeks of therapy (Reference 36). During treatment with metformin, a baseline serum creatinine level is recommended. Metformin is contraindicated if serum creatinine levels are greater than 1.4 mg/dL and 1.5 mg/dL in females and males, respectively (Reference 43). It is also not recommended for use in those with hepatic disease (Reference 43).

Conclusions

Many challenges exist in the prevention and treatment of pediatric obesity. However, assessing BMI at each encounter with a pediatric patient will assist in identifying those who are overweight and obese for the implementation of lifestyle modifications. Early intervention may halt the progression of complications in this population.

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PART IV

Renal/ Endocrinology

Michael Chicella, Pharm.D.

Section Editor

CHAPTER 22

Nephrotic Syndrome

Michael Chicella, Pharm.D.

Learning Objectives

1. Recognize the signs and symptoms of nephrotic syndrome.
2. List the three common pathologic types of nephrotic syndrome.
3. Explain the treatments that can be used to control edema associated with nephrotic syndrome.
4. Discuss the drug treatments used to induce remission and prevent relapse of nephrotic syndrome.
5. Discuss the adverse drug effects associated with drug treatments used in nephrotic syndrome.
6. Discuss the prognosis associated with nephrotic syndrome.

Abbreviations in This Chapter

ACE	Angiotensin-converting enzyme
ARB	Angiotensin type II receptor blocker
HMG-CoA	Hydroxymethylglutaryl coenzyme A

Introduction

Nephrotic syndrome is one of the more common childhood kidney diseases. It is characterized by edema, proteinuria, and hypoalbuminemia that cycle through periods of exacerbation and remission. Proper diagnosis and treatment of nephrotic syndrome are essential because it is associated with a spectrum of clinically important sequelae that can progress to end-stage renal disease if not properly managed.

Epidemiology

Nephrotic syndrome affects 16 in 100,000 children, making it one of the more common childhood kidney diseases (Reference 1). Most patients present between 1 and 7 years of age. There is a male predominance in nephrotic syndrome, as there is in chronic kidney disease in general (Reference 2). In addition, African-American and Hispanic children have a greater incidence of disease, a poorer prognosis, and a more rapid progression to renal failure (Reference 3).

Etiology

Nephrotic syndrome can result from any glomerular injury associated with proteinuria. Most cases are idiopathic; however, nephrotic syndrome can be congenitally acquired, or it can develop in patients with other diseases such as Berger's disease, Henoch-Schonlein purpura, systemic lupus erythematosus, and poststreptococcal glomerulonephritis. Nephrotic syndrome has also been associated with infections such as syphilis, hepatitis B, and human immunodeficiency virus. In addition, certain medications, including nonsteroidal anti-inflammatory medications and anticonvulsants, may cause nephrotic syndrome.

There are three common pathologic types of nephrotic syndrome: membranoproliferative glomerulonephritis, focal segmental glomerulosclerosis, and, most commonly, minimal lesion or minimal change disease. Minimal change disease accounts for more than 70% of nephrotic syndrome cases (Reference 1). Patients with minimal change disease generally respond well to corticosteroids and have the most favorable prognosis. Patients with either membranoproliferative glomerulonephritis or focal segmental glomerulosclerosis are generally less responsive to corticosteroids and are at a greater risk of progressing to renal failure (Reference 4).

Clinical Presentation and Diagnosis

The primary clinical features of nephrotic syndrome are proteinuria, hypoalbuminemia, and edema. Hyperlipidemia and hypertension are also often associated with nephrotic syndrome. Some patients may lack one or more of these features; however, both proteinuria and hypoalbuminemia must be present to establish this diagnosis. With respect to edema, most patients present with periorbital, lower extremity, or genital edema. The edema can range from mild localized edema to generalized anasarca. It is generally worse in the morning because of gravitational shifts and sleep position; however, the edema can persist throughout the day. Patients may also report changes in urine appearance (e.g., "foamy urine"). Although urine normally forms bubbles in the toilet, protein acts like a stabilizer and can give urine a beer-like "head" (Reference 5). Once suspected, a urinalysis should be performed looking specifically for proteinuria. Most patients with nephrotic syndrome will have a urine

protein concentration greater than 300 mg/dL; however, a detectable level of protein in the urine lower than 300 mg/dL does not necessarily rule out nephrotic syndrome. Other laboratory analyses including blood urea nitrogen, serum creatinine, serum albumin, cholesterol, antinuclear antibody, and serum complement 3 levels should be measured to rule out other causes of proteinuria. Serum albumin is usually less than 2.5 mg/dL in patients with nephrotic syndrome (Reference 1). Most patients will have a serum cholesterol concentration above 200 mg/dL, and it is not uncommon for patients to have a serum cholesterol concentration of 600 or 700 mg/dL (Reference 5). Some experts recommend a 24-hour urine collection; however, this is difficult to accomplish, especially in children who are not toilet trained. Therefore, collection of the first morning urine to determine a urine protein-to-creatinine ratio is adequate (Reference 1). A urine protein-to-creatinine ratio greater than 2 is indicative of nephrotic syndrome (Reference 6). A renal biopsy can be performed; however, it is usually reserved for patients older than age 12 years at presentation and for patients with steroid-resistant nephrotic syndrome (Reference 1).

Treatment

Treatment response, which can be variable, depends on the pathologic type of nephrotic syndrome. Corticosteroids are the mainstay of treatment for children with nephrotic syndrome, and patients are quickly determined to have either steroid-dependent or steroid-resistant nephrotic syndrome. Steroid-dependent nephrotic syndrome is associated with a good long-term prognosis (Reference 3). Many of these patients can maintain disease remission with low-dose corticosteroids given daily or every other day. Some of these patients may need other medications combined with corticosteroids to maintain remission. Prednisone, or prednisolone, is the corticosteroid commonly used. Depending on the guidelines being used, it may be dosed as milligrams per kilogram or milligrams per square meter. Prednisone is initially dosed at 2 mg/kg/day (60 mg/m^2/day) up to 60 mg/day. It can be given as a single daily dose in the morning or divided into several doses. Although no difference in efficacy exists, there is at least a theoretical advantage to once-daily morning administration. This regimen would mimic the normal diurnal secretion of endogenous adrenal corticosteroids. The initial dose is usually continued for 6 weeks (Reference 1). After symptom resolution, the dose is reduced to 1.5 mg/kg/day (40 mg/m^2/day) and given every other day for 6 weeks. Historically, corticosteroids were tapered off during the next 6 months, provided no recurrence of symptoms occurred; however, newer guidelines indicate that no taper is required after the initial 12 weeks of therapy (Reference 1).

Because of the extensive toxicity profile associated with exogenous corticosteroids, the sooner they can be discontinued, the better. Short-term adverse effects include hyperglycemia, hypertension, and leukocytosis. Long-term adverse effects include the previously mentioned effects plus growth retardation, osteoporosis, peptic ulcer disease, vision changes, behavioral changes, and Cushing syndrome. In addition, children receiving a prolonged course of corticosteroids can develop adrenal gland suppression. Therefore, patients may need to be given "stress" doses of corticosteroids if they are traumatized or infected or if they require surgery. If steroids cannot be discontinued, the goal should be to achieve the lowest possible dose that controls a relapse of symptoms while minimizing toxicity. Therapy response is determined by monitoring the urine protein concentration. Often, the urine protein concentration becomes undetectable within the first few weeks of corticosteroid administration. As the corticosteroid dose is reduced, urine protein should be monitored. Recurrence of proteinuria for 3 or more consecutive days indicates relapse. In patients who experience infrequent relapses, the prednisone dose is increased to 2 mg/kg/day (60 mg/m^2/day) until the urine protein concentration is undetectable for 3 consecutive days. Then, the dose is reduced to 1.5 mg/kg/day (40 mg/m^2/day), given every other day for 4 weeks. In patients who experience relapses more frequently, the same regimen is followed. However, after the 4 weeks of therapy is completed, the prednisone dose is tapered off over 2 months (Reference 1).

Other medications may be added to further reduce the dose of corticosteroids used or to treat patients who relapse frequently. Calcineurin inhibitors such as cyclosporine are often the first of these agents used. Cyclosporine inhibits helper T cell interleukin-2 production and causes renal arteriolar vasoconstriction. It reduces proteinuria by many mechanisms of action. In addition, cyclosporine has antiproteinuric effects by changing glomerular permeability. The usual initial dose of cyclosporine is between 3 and 5 mg/kg/day divided twice daily. Cyclosporine has several adverse drug effects associated with its use; therefore, it should be used at the lowest effective dose possible. Adverse drug effects from cyclosporine include hypertension, hirsutism, electrolyte abnormalities, and nephrotoxicity. In addition, variability exists in bioavailability between various cyclosporine products; therefore, it is usually recommended to avoid switching or substituting one product for another.

Tacrolimus is another calcineurin inhibitor used in nephrotic syndrome. Tacrolimus has inhibitory effects on CD4 helper cells. However, the mechanism behind the efficacy of tacrolimus in nephrotic syndrome is not completely understood. Investigators have shown increased inhibition of vascular permeability with tacrolimus in patients with minimal change disease (Reference 7). The

efficacy of tacrolimus may also be due to its better cytokine inhibition compared with cyclosporine (Reference 8). Regardless of the mechanism, up to 94% of patients with nephrotic syndrome improve while taking tacrolimus. Eighty-one percent of patients experience complete remission of disease (Reference 8). Tacrolimus is initially dosed between 0.05 and 0.1 mg/kg/day divided twice daily. Adverse drug effects associated with tacrolimus include hypertension, altered mental status, electrolyte abnormalities, and nephrotoxicity. Similar to cyclosporine, tacrolimus is nephrotoxic and should be used cautiously in patients with progressive renal dysfunction.

Mycophenolate mofetil is another immunomodulatory agent that is effective in the management of nephrotic syndrome. Mycophenolate is a purine synthetase inhibitor, not a calcineurin inhibitor. It has an active metabolite, mycophenolic acid, which inhibits the synthesis of T- and B-cell lymphocytes. In addition, mycophenolate inhibits vascular smooth muscle and mesangial cell proliferation, inhibits nitric oxide synthase, and induces apoptosis in activated T cells. One or more of these actions account for the effects seen in patients with nephrotic syndrome (Reference 9). Mycophenolate is initially dosed between 24 and 36 mg/kg/day divided twice daily. Adverse drug effects associated with its use include dyspepsia, diarrhea, leukopenia, and rarely lymphoma. Because nephrotoxicity is less likely with mycophenolate than with cyclosporine or tacrolimus, it may be a good alternative in patients with progressive renal insufficiency.

Cytotoxic agents such as cyclophosphamide and chlorambucil may also be used to reduce the risk of relapses without corticosteroids. Furthermore, studies have shown that the use of cytotoxic agents can extend remission by 1 year or longer (References 10, 11). These agents act by interfering with DNA by inserting alkyl chains onto purine bases, thereby causing separation during cell division. They also destroy cells by interfering with nucleic acid synthesis. Cyclophosphamide is initially dosed 2–3 mg/kg/day orally given once a day. The effectiveness of cyclophosphamide at inducing remission and reducing relapse appears to be related to the length of treatment. The optimal length of treatment appears to be 8–12 weeks (Reference 12). Chlorambucil is less commonly used than cyclophosphamide; however, when used, it is usually dosed at 0.1–0.2 mg/kg/day given once daily for 6–8 weeks (Reference 13). Alkylating agents also have significant adverse drug effects that must be weighed against their potential benefits. These include nausea and vomiting, alopecia, growth retardation, bone marrow suppression, cystitis (cyclophosphamide), and seizures (chlorambucil). Children receiving alkylating agents are also at greater risk of both viral and bacterial infections.

Some patients with nephrotic syndrome have steroid-resistant disease. The pharmaceutical management of these patients is much more difficult. Steroid resistance puts the patient at greater risk of developing complications associated with nephrotic syndrome and progression to end-stage kidney disease. The optimal therapy for steroid-resistant nephrotic syndrome remains poorly defined. Commonly used medications include calcineurin inhibitors, mycophenolate mofetil, and the cytotoxic agents. Non-immunosuppressive agents are also considered in these patients. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin type II receptor blockers (ARBs) have been shown to have an antiproteinuric effect in adults with glomerular diseases (Reference 14). Case series and small studies are available that suggest a reduction in proteinuria in children with nephrotic syndrome (References 15, 16). The mechanism responsible for the antiproteinuric effects of the ACE inhibitors is not clearly defined. Reduction of systemic and intraglomerular pressures and improved size selectivity of the glomerular basement membrane may contribute to this effect (Reference 17). In addition, because many children with nephrotic syndrome also present with hypertension, an ACE inhibitor or an ARB helps control blood pressure until disease remission is achieved. Enalapril, an ACE inhibitor, has been shown to reduce proteinuria in children with steroid-resistant nephrotic syndrome (Reference 17). Enalapril should be initiated at a dose of 0.2 mg/kg/day. Its effectiveness appears to be dose related, so its dose should be increased to a goal dose of 0.5–0.6 mg/kg/day (Reference 17). Fosinopril is another ACE inhibitor that has been shown to reduce proteinuria and renal tubular damage in children with nephrotic syndrome (Reference 18). When initiating an ACE inhibitor, or an ARB, serum electrolytes including serum creatinine should be monitored periodically.

The use of B cell–depleting therapy, rituximab, is increasing in patients with nephrotic syndrome. Rituximab is a chimeric monoclonal antibody with activity against the CD20 surface antigen of B cells. A single dose of rituximab of 375 mg/m^2 has been shown to be effective in children with steroid-dependent and steroid-resistant nephrotic syndrome. Treatment may have to be repeated, if necessary (Reference 19). Adverse drug effects from rituximab can include infusion-related reactions, such as fever, hypotension, rash, and bronchospasm. The adverse effect of most concern, however, is rituximab-associated lung injury, or RALI (Reference 20). Although the pulmonary injury associated with rituximab is often transient and reversible, it can be associated with potentially fatal pulmonary injuries like interstitial pneumonitis, pulmonary fibrosis, and bronchiolitis obliterans (Refer-

ence 21). A chest radiograph should be checked before starting rituximab treatment and periodically during and after treatment because the time to onset of symptoms ranges from 1 to 3 months (Reference 21).

Supportive Therapy

The goal of supportive therapy is to control edema until remission can be achieved. Edema should be reversed slowly. To begin, dietary sodium intake should be restricted. Although restricted sodium intake is recommended, most patients have difficultly adhering to a low-sodium diet because they are less palatable than regular diets. In general, a 1-g sodium diet is recommended for younger children, and a 2-g diet is recommended for older children and adolescents. It may be possible to manage mild edema in this way. For patients with severe edema, or anasarca, diuretic therapy is often used. A loop diuretic such as intravenous furosemide is usually chosen. Furosemide is initially dosed as 1 mg/kg/dose; however, higher doses of furosemide are often required to achieve effective intratubular concentrations (Reference 22). This is because furosemide is bound to albumin in the tubular lumen of patients with proteinuria. In addition, many clinicians will give intravenous albumin before diuretic administration, although data showing improved diuresis with sequential dosing of albumin and furosemide versus furosemide alone are lacking (References 23, 24). Albumin is administered as 25% albumin, initially dosed as 0.5–1 g/kg per dose. It is given to increase the oncotic pressure and draw fluid into the intravascular space from the interstitium. Albumin is followed by furosemide. Sequential dosing of furosemide and albumin may be repeated as often as every 6 hours, depending on the patient's clinical status and response.

Patients with nephrotic syndrome are at greater risk of developing thromboembolic complications such as pulmonary embolism and deep venous thrombosis. Renal venous thrombosis is also seen in 20% to 30% of adults with membranoproliferative glomerulonephritis (Reference 25). The factors that may contribute to the risk of thromboembolic complications in nephrotic syndrome include low factor IX and factor XI levels, increased factor V and factor VIII, decreased antithrombin III, and increased platelet reactivity (Reference 22). Most of this information is from adult data, and it is difficult to extrapolate this information to children. As children get older, or if the patient has other risk factors for thromboembolic complication, they may benefit from prophylactic anticoagulant therapy. Refer to the Anticoagulation chapter for further information on appropriate anticoagulation management.

Children with nephrotic syndrome are also at increased risk of bacterial infections, particularly pneumococcal peritonitis. This is because patients with nephrotic syndrome have low levels of endogenous immune globulin. Children with nephrotic syndrome should be kept up to date on their vaccines, especially pneumococcal vaccines (Reference 26). The administration of intravenous immune globulin to maintain serum immunoglobulin G levels greater than 600 mg/dL may also help reduce the rate of bacterial infections in these children (Reference 27).

Hyperlipidemia associated with nephrotic syndrome may increase the risk of atherosclerosis and cardiovascular complications. A diet limiting fat to less than 30% of calories, saturated fat to less than 10% of calories, and cholesterol to less than 300 mg/day is recommended (Reference 1). Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors can be used to manage hyperlipidemia in patients whose condition cannot be controlled by diet alone. There is also evidence that HMG-CoA reductase inhibitors decrease proteinuria and thus decrease renal injury (Reference 28). To date, two prospective studies have been performed to assess the efficacy of HMG-CoA reductase inhibitor therapy in children with steroid-resistant nephrotic syndrome (References 29, 30). Because some HMG-CoA reductase inhibitors may interact with other medications often used in nephrotic syndrome, such as the calcineurin inhibitors, this is an important consideration before beginning a new medication.

Prognosis

The prognosis depends on the pathologic type of nephrotic syndrome and on whether the patient has steroid-dependent or steroid-resistant disease. Children with minimal change disease generally respond well to treatment, with the best prognosis and the fewest disease-related complications. Conversely, patients with focal segmental glomerulosclerosis can develop considerable glomerular scarring, leading to end-stage renal disease and ultimately resulting in transplantation (Reference 31). Similarly, patients with steroid-resistant disease are at greater risk of developing progressive kidney injury than patients with steroid-dependent disease (Reference 1). Regardless of the type of nephrotic syndrome, exacerbations can occur in most patients throughout life, and many of these patients will eventually become steroid-dependent (Reference 32).

Conclusions

Nephrotic syndrome is a chronic disease that begins in childhood and continues throughout life. It is characterized by periods of remission and exacerbation. For many patients, it can be controlled with the use of corticosteroids; however, in some patients, other

medications with significant adverse drug reaction profiles need to be used. Hence, the pharmacist should play an integral role in the pharmaceutical management of children with nephrotic syndrome.

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CHAPTER 23

Osteogenesis Imperfecta

Michael Chicella, Pharm.D.

Learning Objectives

1. Compare and contrast the seven pathologic types of osteogenesis imperfecta (OI).
2. Describe the prognosis of OI.
3. List the signs and symptoms of OI.
4. Describe the use of calcitonin in the management of OI.
5. Describe the use of bisphosphonates in the management of OI.

Abbreviation in This Chapter

OI	Osteogenesis imperfecta

Introduction

Osteogenesis imperfecta (OI), historically referred to as brittle bone disease, is a rare genetic bone disorder. It is a heterogeneous group of conditions characterized by bone fragility and decreased bone mass. The classic and most common manifestations of OI are categorized as four types: I–IV. Patients with these four types of OI have mutations in the type I or type II collagen (*COLIA1, COLIA2*) genes. These mutations are caused by autosomal dominant genetic derangements of collagen type I, which is the main protein found in bone. Collagen type I contributes to cortical thickness and bone strength. Recently, other types of OI that have no collagen mutation were identified. Type V is also caused by an autosomal dominant genetic derangement. The mode of inheritance of type VI is unknown; type VII is caused by an autosomal recessive disorder. Type VII has only been reported in First Nations people in Quebec (Reference 1).

Individuals with OI suffer from recurrent fractures. Patients who live into adulthood experience chronic bone pain, deformities, and disabilities. Caring for these patients can be challenging for families and caregivers. In the most extreme cases, even minor activities, such as changing diapers or cuddling, can result in fractures if not done with the utmost care. As children with OI grow older, traditional childhood activities like playing football, jumping on a trampoline, or playing on playground equipment can result in significant injury. Parents and caregivers can find it difficult to allow their children to be "normal" while protecting them from injury.

Epidemiology

Osteogenesis imperfecta occurs in about 1 of every 20,000 births, and according to the Osteogenesis Imperfecta Foundation, between 20,000 and 50,000 people in the United States have OI (Reference 2). There is no ethnic or sex-based predisposition to OI. Because most types of OI are caused by a dominant genetic mutation, most patients will have a parent with a diagnosis of OI. However, around 25% of children with OI are born into a family with no history of OI (Reference 2). The diagnosis of OI is usually made in infancy; however, some mild forms of the disease may not be diagnosed until later in childhood.

Pathophysiology

The pathophysiology of OI with collagen type I molecule mutations (types I–IV) is best understood and is discussed in this section. Very little is known about the pathogenesis of OI types V–VII (Reference 3). Collagen type I molecules consist of three polypeptide chains — two alpha 1 and one alpha 2 chains. These chains twist to form a triple-helical structure. For the chains to intertwine correctly, they must have a glycine residue at every third position. Substitution at the glycine residues can result in abnormalities and produce a mixture of normal and abnormal collagen strands. Abnormal collagen has lower tensile strength, resulting in brittleness of the bones (Reference 4).

Clinical Presentation

The presentation of OI varies according to the age of the patient at diagnosis and the type of disease the patient has. The clinical features of each type are outlined in Table 1. Patients may present asymptomatically or with classic signs of OI such as blue sclera and a history of fractures and wormian bones (extra bone pieces in the suture lines of the skull). The severity of illness also depends on the type of OI. Severity increases in the following order: type I < IV, V, VI, VII < type III < type II (Reference 3).

Type I is the most common form of the disease and is considered the mildest. Patients with OI type I have minimal bone deformities. Fractures usually involve

Table 1. Types of Osteogenesis Imperfecta

Type	Severity	Clinical Features
I	Mildly deforming	Normal height, blue sclera
II	Life threatening	Rib and long bone fractures at birth, severe deformities, dark or blue sclera
III	Severely deforming	Very short stature, triangular face, scoliosis, blue to gray sclera, dentinogenesis imperfecta
IV	Moderately deforming	Short stature; scoliosis; gray, blue, or white sclera; dentinogenesis imperfecta
V	Moderately to severely deforming	Short stature, dislocated radial head, calcification of interosseous membrane, hyperplastic callus
VI	Moderately to severely deforming	Short stature, scoliosis, accumulation of osteoid in bone tissue, fish-scale pattern of bone lamellation imperfect
VII	Moderately to severely deforming	Short stature

Adapted from Reference 3.

the long bones; however, vertebral compression fractures can also occur, especially during periods of rapid growth such as puberty.

Patients with OI type II are at high risk of dying during the perinatal period. These patients develop several fractures, both in utero and during the birth process. Many patients die of respiratory distress or failure secondary to rib fractures. Theoretically, fractures could potentially be minimized by delivering the baby by cesarian section if OI is diagnosed before delivery; however, literature showing that cesarian sections reduce fractures or improve mortality is lacking (Reference 5). Patients with OI type II also have bone deformities. Their bones have low mineral density and are usually short and broad.

Children with OI type III usually do not survive past the newborn period. These patients typically suffer from fractures even after mild trauma and develop bone deformities involving the long bones and vertebras. Because of this, children with OI type III are unable to walk and will require mobility assistance with a wheelchair. They may also have mandibular deformities, giving the child a triangular face. Similar to patients with OI type II, patients with OI type III die of respiratory failure associated with rib fractures. Other manifestations of OI common to types I–III include dentinogenesis imperfecta (tooth abnormalities), hyperlaxity of ligaments, and wormian bones. Most of these patients will also have bluish sclera because of abnormal collagen formation.

The presentation of patients with OI type IV varies greatly. Patients may experience very few fractures, or they may experience multiple fractures even after the most minor trauma. These patients may be ambulatory, or they may require a wheelchair for mobility. Patients with type IV also have dentinogenesis imperfecta and bluish sclera. The more severe the variant of OI type IV, the poorer the patient's prognosis.

Patients presenting with OI types V–VII share similar physical presentations. These patients are short in stature. Unlike patients with other types of OI, these patients do not have dentinogenesis imperfecta. In addition, patients with types V–VII do not have sclera discoloration because normal collagen makes normal sclera white.

Complications/Prognosis

During infancy, patients with OI present with several unexplained fractures and are often suspected of being victims of non-accidental trauma or child abuse. Although this should be in the differential diagnosis, health care professionals are cautioned not to wrongly accuse parents or caregivers of wrongdoing.

In childhood, as patients with OI learn to stand and walk, fractures become more common. Children with more severe forms of OI can have severe bowing of their long bones; therefore, they may have difficulty walking or be unable to walk at all. Similar to patients who present during infancy, patients who present with OI during childhood are potentially misdiagnosed and thought to be victims of non-accidental trauma or child abuse.

During adolescence and the teenage years, patients experience periods of rapid bone growth and are at high risk of developing fractures. Both long bone fractures and vertebral fractures can occur. Vertebral fractures are often initially misdiagnosed as "growing pains," back pain, and even scoliosis.

For patients with OI who survive into adulthood, the incidence of fractures tends to decrease. This occurs for many reasons. First, the bones have matured and are not undergoing instability associated with growth (Reference 6). Second, by adulthood, most patients with OI limit their exposure to situations in which bodily injury is likely. Adults with OI, however, are not without complications of their disease. They can suffer from chronic bone pain. In addition, patients with OI can develop hearing loss caused by the involvement of the bones in the inner ear. Although hearing loss is an uncommon complication in infants and children, it can occur in up to 50% of adults with OI (Reference 7).

The prognosis of the patient depends on the type of OI and the patient's clinical course. In general, the prognosis is poor, and most patients suffer from recurrent fractures, bone deformities, chronic bone pain, and disabilities. Surgical and medical treatments are often required continuously or intermittently for the duration of life. Unfortunately, for patients with OI, no cure is available for this life-threatening disease.

Diagnosis

There are no standard diagnostic criteria for OI (Reference 1). Osteogenesis imperfecta can be diagnosed antenatally because bone demineralization is detectable by ultrasonography as early as 13–14 weeks' gestation (Reference 6).

Postnatally, the diagnosis is based on clinical presentation. Analysis of serum laboratory values does not help, although some laboratory values, such as serum alkaline phosphatase, can help differentiate OI from other, similar diagnoses such as idiopathic hyperphosphatasia, hypophosphatasia, or rickets. In patients with OI, the serum alkaline phosphatase is usually normal or on the upper end of the normal range for age, whereas in other bone diseases, alkaline phosphatase concentrations can be markedly elevated (Reference 8).

Gene analysis can be used to identify mutations in the gene responsible for encoding collagen type I, *COL1A1* or *COL1A2*. Either blood or saliva can be analyzed for *COL1A1* or *COL1A2* gene mutations (Reference 9). Alternatively, a skin biopsy to determine the amount and type of type I procollagen present in the skin fibroblasts can be used to diagnose OI (Reference 10). These tests can detect around 90% of collagen type I mutations (Reference 11). Although a positive study leads to the diagnosis of OI, a negative study cannot rule out types V–VII because they are not associated with a collagen type I mutation.

Therapy Goals

Currently, there is no cure for OI, and the variety of mutations responsible for this disease make a cure in the near future unlikely. Therefore, the goals of treatment, whether nonpharmacologic or pharmacologic, are to support bone structure, avoid bone fractures, and promote bone strength.

Nonpharmacologic Treatment

Historically, supportive treatments such as orthopedic procedures and physical therapy were the cornerstones of treatment. Orthopedic procedures of inserting rods and braces have been used to strengthen bones and minimize or correct deformities. Physical therapy and assistive devices are used to increase muscle strength and expand range of motion. However, physical therapy can be a painful experience for many of these patients. In addition, patients with severe forms of OI may be too fragile to perform range-of-motion exercises.

Pharmacologic Therapy

No standard first-line medication is recognized for OI management. Various treatments have been attempted, including hormones, anabolic steroids, vitamins, and minerals. Even highly toxic agents such as arsenic and hydrochloric acid have been tried. Unfortunately, none of these treatments has consistently shown efficacy (Reference 12).

Calcitonin has been shown to decrease the number of fractures experienced annually by patients with OI types I–III (References 13–15). In addition, in one study, patients showed an increase in the ability to stand and move and reported a subjective feeling of strength in their lower extremities during calcitonin therapy (Reference 15). Calcitonin works by inhibiting osteoclast activity, thereby inhibiting bone resorption. It is available as an injection that can be given either intramuscularly or subcutaneously, and there is an intranasal solution. Both have been used in patients with OI. Dosing for the intramuscular or subcutaneous injection is 2 international units/kg three times/week (Reference 15). Intranasal calcitonin is dosed as follows. Patients weighing less than 20 kg receive 50 units intranasally, and patients weighing more than 20 kg receive 100 units intranasally. It is administered twice weekly for 2 weeks, followed by 2 weeks of no therapy (Reference 13). Calcitonin therapy has been continued safely for 76 months (Reference 13). Case reports have associated calcitonin therapy with electrolyte derangements such as hypophosphatemia, hypokalemia, hyponatremia, and

hypomagnesemia (Reference 16). Therefore, electrolytes should be monitored periodically while the patient is receiving calcitonin.

The bisphosphonates are clinically useful in the setting of OI, despite the lack of large randomized controlled trials supporting their safety and efficacy. The bisphosphonates inhibit osteoclast bone resorption, thereby increasing bone formation. Bisphosphonates bind to calcium in bone because their structure is similar to pyrophosphate. Osteoclasts absorb the calcium and bisphosphonate. The bisphosphonates inhibit farnesyl-pyrophosphate synthase, an enzyme involved in the synthesis of intracellular proteins. By inhibiting protein synthesis, the bisphosphonates decrease the ability of lipids to attach to and form cell membranes of osteoclasts, thereby ultimately causing osteoclast cell death (Reference 17).

Studies that have evaluated bisphosphonate use in children with OI have shown that bisphosphonates significantly improve bone density (References 18–23). One study showed a mean bone density increase of 41% per year while patients were on bisphosphonate therapy (Reference 23). During treatment, studies have shown that vertebral bone mass increases faster in the bisphosphonate group than in the controlled group (Reference 24). Bisphosphonates also reduce the risk of fractures (References 18, 19, 22) and increase strength (Reference 25). One study showed that the incidence of fractures decreased from 2.3 ± 2.2 per year before bisphosphonate treatment to 0.6 ± 0.5 per year during treatment (Reference 23). Bisphosphonates, however, neither completely eliminate the risk of fractures nor cure OI (Reference 26).

Pamidronate has been studied in children with severe OI (References 23, 27, 28). It is administered as a 4-hour infusion, on a cyclic schedule, the frequency of which varies according to the patient's age (Reference 3). Children younger than 2 years receive 0.5 mg/kg/day intravenously for 3 days repeated every 2 months. Children older than 2 years but younger than 3 years receive 0.75 mg/kg/day intravenously for 3 days repeated every 3 months. Patients 3 years and older should receive 1 mg/kg/day intravenously, up to a maximum of 60 mg/day, for 3 days and then repeated every 4 months.

Risedronate and zoledronate have also been studied. Similar to pamidronate, zoledronate is administered intravenously. In one study of patients with OI type III, children younger than 6 months were given 2 mg intravenously over 15 minutes every 3–4 months, and patients older than 6 months were given 4 mg intravenously over 15 minutes every 3–4 months (Reference 29).

Risedronate has been used in children with mild to severe OI. A potential advantage of risedronate compared with the other bisphosphonates is that it can be administered enterally (References 17, 30). Children weighing less than 40 kg receive 15 mg orally once weekly, and children weighing more than 40 kg receive 30 mg orally once weekly (Reference 30). Other investigators indicate that the efficacy of risedronate may be dose-dependent and that a higher dose (2 mg/kg once weekly) increases bone mass and reduces bone deformities more significantly than lower doses (0.2 mg/kg or 1 mg/kg) (Reference 17).

Several potential adverse drug effects are associated with bisphosphonate use. Acute-phase reactions such as fever, muscle aches, and vomiting can occur in up to 85% of patients (Reference 28). These reactions usually occur with the initial dose; however, they can occur with subsequent doses and with dose changes. Acute-phase reactions primarily occur with intravenous infusions; however, acute reactions associated with the oral administration of bisphosphonates have also been reported (Reference 28). If acute-phase reactions occur, a lower dose may be administered to determine whether this will alleviate reactions. There are also case reports of mandibular osteonecrosis associated with bisphosphonate therapy (Reference 31), which commonly presents as jaw pain. Although many patients with OI will be followed by a dentist, patients receiving bisphosphonate therapy should have semiannual dental examinations. In addition, there have been reports of severe symptomatic hypocalcemia associated with intravenous bisphosphonate therapy; however, none of the reports involved patients with OI (References 32, 33). Respiratory distress has also been associated with bisphosphonate therapy in children with OI (Reference 34). One study reported that 7% of infants with type III OI developed respiratory distress during their first pamidronate infusion. Two infants in this study required intensive care, and all the infants had a history of respiratory distress. The etiology of this is unknown, but it is hypothesized that respiratory distress is caused by tumor necrosis factor release or acute bronchospasm or that it is associated with the volume of fluid administered during pamidronate infusion. Therefore, pamidronate should be used with caution in infants with OI and a history of acute respiratory distress.

Zoledronate has been associated with renal dysfunction, including renal failure. Renal failure can occur after a single infusion of zoledronate, or it can occur after several infusions. Additional risk factors for renal dysfunction include underlying renal impairment, concomitant nephrotoxin use, concurrent use of diuretics, and dehydration. Patients receiving zoledronate should have their renal function monitored periodically while receiving treatment.

Oral bisphosphonates like risedronate have been associated with the development of esophagitis and esophageal cancer. Patients taking risedronate should take it first thing in the morning and remain upright

for at least 30–60 minutes after the dose. Any swallowing difficulties, chest pain, or heartburn may indicate signs of esophageal problems; these should be reported to their health care provider.

Questions remain to be answered before bisphosphonate treatment can be recommended for all children with OI. In children with recurrent, low-trauma fractures, the benefits of bisphosphonate therapy may outweigh the risks associated with therapy. However, the role of bisphosphonates in children with mild OI and infrequent fractures is unclear (Reference 28). In addition, the appropriate length of bisphosphonate therapy and the time to terminate treatment need to be elucidated (Reference 28). A few children with OI have been treated for up to 9 years with monthly doses of pamidronate without experiencing long-term adverse effects (Reference 24).

Conclusions

Osteogenesis imperfecta is a rare genetic disorder of the bone. Individuals with OI suffer from recurrent fractures throughout their lives. Patients who live into adulthood experience life with chronic bone pain, deformities, and disabilities. At present, there is no pharmacologic cure for OI. Calcitonin has been associated with a reduced risk of fractures, and the bisphosphonates, specifically pamidronate, have been associated with improved bone density and reduced risk of fractures.

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CHAPTER 24

Diabetes Mellitus

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Learning Objectives

1. Differentiate the pathophysiology between type 1 and 2 diabetes mellitus (DM) in pediatric patients.
2. List the criteria for the diagnosis of DM in pediatric patients.
3. Describe acute and chronic complications of DM in pediatric patients.
4. Develop an insulin regimen for a pediatric patient.
5. Discuss the available pharmacologic agents for the treatment of type 2 DM in pediatric patients.

Abbreviations in This Chapter

BG	Blood glucose
CSII	Continuous subcutaneous insulin infusion
DDP-IV	Dipeptidyl peptidase IV enzyme
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
ESRD	End-stage renal disease
GLP-1	Glucagon-like peptide-1
HHS	Hyperosmolar hyperglycemic syndrome
PG	Plasma glucose
SMBG	Self-monitoring of blood glucose

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases in pediatrics. Either a lack of insulin release from the pancreas or a resistance to insulin in peripheral tissues, resulting in hyperglycemia, causes DM. Persistent hyperglycemia leads to several acute, microvascular, and macrovascular complications necessitating metabolic control with pharmacologic treatment. Children and adolescents present unique challenges in achieving metabolic control. This chapter will focus on such challenges and appropriate pharmacotherapy strategies in pediatric patients.

Epidemiology

Ongoing prevalence estimates 1.82 cases of some form of DM per 1,000 youths in the United States. The overall prevalence of DM increases with increasing age, with rates reaching 3.35 cases per 1,000 youths aged 15–19 years in 2001 (Reference 1). Although type 1 DM accounts for most diabetes in pediatrics, the number of children and adolescents with type 2 DM is increasing (Reference 1).

Classification

It is necessary to classify diabetes upon diagnosis to initiate appropriate pharmacologic treatment. Before the 1990s, most DM cases diagnosed in youth were type 1. However, because of increases in obesity rates, pediatric patients are now presenting with type 2 DM (Reference 2). Youths can also be affected with other forms of diabetes, including maturity-onset diabetes of youth; neonatal diabetes; mitochondrial diabetes; diabetes associated with lipodystrophy; diabetes secondary to other pancreatic, endocrine, or genetic syndromes; or drug-induced diabetes (e.g., corticosteroids, immunosuppressants) (Reference 3). This chapter will focus on the two most common forms of DM in pediatrics, types 1 and 2. Table 1 highlights differences between type 1 and 2 DM.

Pathophysiology

Type 1 DM is the result of a T-cell–mediated autoimmune attack on the beta cells of the pancreas, resulting in complete insulin deficiency. Individuals with type 1 DM typically have a genetic predisposition, indicated by the presence of human leukocyte antigens. The *DR3-DQ2* and *DR4-DQ8* alleles are associated with increased risk, whereas the *DR2-DQ6* allele is protective against type 1 DM (Reference 5). The T-cell–mediated attack on the beta cells results in an inflammatory process in the islets of Langerhans and the production of antibodies. Antibodies to insulin, glutamic acid decarboxylase, and the protein tyrosine phosphotase are detectable even before the clinical presentation of disease. The autoimmune process can take months to years to occur. Signs of insulin deficiency do not become evident until about 80% of the beta cells are destroyed. Typically, the earlier the onset of destruction, the more rapidly insulin deficiency is evident. Although controversial, it is believed that in addition to a genetic predisposition, an environmental toxin contributes to the development of type 1 DM. Environmental factors thought to trigger

Table 1. Characteristics of Type 1 and Type 2 Diabetes Mellitus in Children and Adolescents (Reference 4)

	Type 1	Type 2
Age of presentation	Throughout childhood	Typically at puberty
Onset	Acute	Insidious to severe
Ketosis at onset	Common	Variable
Affected relative	5%	75% to 90%
Female/male	1:1	2:1
HLA[a] DR3, DR4	Increased association	No association
Ethnicity	All, whites	All
Insulin secretion	Decreased/absent	Variable
Insulin sensitivity	Normal when controlled	Decreased
Insulin dependence	Permanent	Episodic
Obesity	< 24%	> 90%
Acanthosis nigricans	No	Common
Pancreatic autoantibodies	Yes	No

[a]Human leukocyte antigen-DR.
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type 1 DM include certain foods (e.g., cow's milk, nitrosamines) or viral infections (e.g., enterovirus, rotavirus). To date, only exposure to congenital rubella has been associated with the onset of type 1 DM.

Type 2 DM results from both impaired insulin secretion from the pancreas and insulin resistance. Various factors increase the susceptibility to decreased insulin sensitivity, including family history, obesity, physical inactivity, diet, and intrauterine factors (Reference 4). Most pediatric patients with a diagnosis of type 2 DM have at least one first- or second-degree relative with type 2 DM. Infants who are born to mothers with gestational diabetes or who are small for gestational age have an increased risk of insulin resistance. The decrease in insulin sensitivity initially leads to an increase in insulin secretion, compensatory hyperinsulinemia, and ultimately beta-cell destruction. Before clinical presentation of type 2 DM, children and adolescents present with hyperinsulinemia or signs of insulin resistance such as acanthosis nigricans. Acanthosis nigricans is a dermatologic disorder characterized by brown to blackish, raised, velvety lesions usually found in skinfolds or creases in the back of the neck, axilla, and genital area (Reference 6). Acanthosis nigricans is thought to be the result of increased insulin levels binding insulin-like growth factor receptors, fibroblasts, and keratinocytes, resulting in the proliferation of epidermal cells (References 6, 7). During puberty, insulin resistance worsens, precipitating glucose intolerance and, subsequently, clinical manifestations of type 2 DM.

Screening

Typically, the time from abnormal glucose control to clinical symptoms of disease occurs fairly rapidly in type 1 DM; therefore, routine screening is not recommended. However, the American Diabetes Association recommends screening for type 2 DM (Reference 8). Children and adolescents who are overweight (defined as a body mass index percentile greater than 85 for age and sex) with two additional risk factors are recommended for screening. Additional risk factors include having a family history of type 2 DM in a first- or second-degree relative, being of a racial/ethnic group with high rates of type 2 DM (i.e., American Indian, African American, Hispanic, Asian, Pacific Islander), or showing evidence of existing insulin resistance. Conditions associated with insulin resistance include acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, and maternal history of gestational diabetes during the child's gestation (References 8). Screening consists of a fasting plasma glucose (PG) or an oral glucose tolerance test every 2 years starting at age 10 or at onset of puberty in any child or adolescent meeting these criteria.

Clinical Presentation and Diagnosis

The classic signs and symptoms of diabetes are polydipsia, polyuria, polyphagia, and weight loss. Those presenting with type 1 DM may have symptoms for 1 month to several months before diagnosis. Female patients with type 2 DM might present with candidal vulvovaginitis in addition to classic symptoms. Although it is more common for a patient with type 1 DM to present with diabetic ketoacidosis (DKA), patients with type 2 DM are still at risk of developing DKA. Other potential findings on presentation include glycosuria and ketonuria. Of note, however, DM can also present asymptomatically in both types 1 and 2, and its presence can be discovered coincidentally with routine laboratory analysis.

Diagnostic criteria for DM include at least one of the following (References 8, 9):

1. Fasting PG of 126 mg/dL or greater;
2. Two-hour PG of 200 mg/dL or greater during an oral glucose tolerance test; or
3. Random PG of 200 mg/dL or greater and symptoms of hyperglycemia.

A fasting PG of 126 mg/dL or greater or a 2-hour PG of 200 mg/dL or greater is repeated for confirming the diagnosis. To differentiate between type 1 and 2 DM, it is recommended to measure islet autoantibodies, insulin, and C-peptide. The presence of islet autoantibodies is indicative of type 1 DM. Interpretation of insulin and C-peptide can be less conclusive because both may still be present in a person with an early diagnosis of type 1 as well as in those with type 2 DM (Reference 9).

Complications

Diabetes mellitus in children and adolescents is associated with short- and long-term complications. Short-term complications include hypoglycemia, DKA, and hyperosmolar hyperglycemic syndrome (HHS). Long-term microvascular complications include retinopathy, nephropathy, and neuropathy. Macrovascular disease, including peripheral, cerebrovascular, and cardiovascular disease, are also long-term complications of DM. Common comorbidities with type 1 DM include thyroid and celiac disease.

Hypoglycemia

Hypoglycemia is experienced in patients treated with insulin for DM. Severe hypoglycemia has been estimated to occur 8–30 times per 100 patient-years of diabetic exposure (Reference 10). Children and adolescents are at higher risk of severe hypoglycemia than are adults because of the lack of symptom recognition, inability to communicate symptoms to the caregiver, and variable eating and exercise habits (Reference 9). Young children tend to be most at risk for severe complications from frequent or severe episodes of hypoglycemia (Reference 9). Hypoglycemia in children can be associated with seizures, acute and chronic impaired cognitive function, coma, and death. Signs, symptoms, and treatment strategies for hypoglycemia will be discussed later in the chapter.

Diabetic Ketoacidosis

Diabetic ketoacidosis results from lack of insulin and increases in counterregulatory hormones (e.g., glucagon, catecholamines, cortisol, growth hormone), resulting in a catabolic state (Reference 11). Diabetic ketoacidosis is characterized by hyperglycemia, acidosis, ketonemia, and ketonuria (Reference 12). Around 29% and 10% of patients with type 1 and 2 DM, respectively, will present with DKA at initial diagnosis (Reference 13). Other factors that precipitate DKA after diagnosis are insufficient exogenous insulin administration, sepsis, trauma, or excessive diarrhea and vomiting (Reference 12). Complications of DKA can include death, usually caused by cerebral edema. Additional causes of death in DKA include other neurologic complications, hypokalemia, hyperkalemia, thrombosis, sepsis, aspiration pneumonia, and pulmonary edema. Long-term complications may include neurologic deficits. Diabetic ketoacidosis will be discussed more thoroughly later in the chapter.

Hyperosmolar Hyperglycemic Syndrome

Hyperosmolar hyperglycemic syndrome is a rare but life-threatening complication of uncontrolled type 2 DM. The incidence of HHS in pediatric patients is unknown, but it is estimated that 4% will present with HHS at time of diagnosis with type 2 DM (Reference 14). Similar to DKA, HHS is characterized by hyperglycemia and hyperosmolarity but not acidosis, ketonemia, and ketonuria (Reference 15). Complications of HHS include thrombosis, rhabdomyolysis, malignant hyperthermia-like syndrome, and death. Death results from severe dehydration, electrolyte imbalance, and hypertonicity (Reference 15).

Retinopathy

Retinopathy results from damage to the blood vessels of the retina. It is the most common cause of adult blindness in the United States. Nonproliferative retinopathy (background retinopathy) is transient and consists of microaneurysms and pre- and intraretinal hemorrhages (Reference 16). Nonproliferative retinopathy is not associated with vision loss and does not always progress to proliferative retinopathy. Proliferative retinopathy is

a severer form of retinopathy and is characterized by the development of new blood vessels, which may rupture or bleed into the vitreoretinal space. Visual loss may occur with proliferative retinopathy (Reference 16).

Retinopathy can be present in children and adolescents within 1–2 years after diagnosis of DM, although it is not usually seen for 5–10 years. It occurs in pediatric patients of all ages, but it tends to present postpubertally. Proliferative retinopathy does not typically present in those younger than 20 years. Risk factors for retinopathy include poor glycemic control, longer duration of diabetes, elevated blood pressure, smoking, hyperlipidemia, albuminuria, and pregnancy (Reference 9). Annual ophthalmologic examinations are recommended when the child is at least 10 years old and has had diabetes for 3–5 years (Reference 9).

Nephropathy

End-stage renal disease (ESRD) requiring dialysis or transplantation is a microvascular complication of DM. The first clinical signs of diabetic nephropathy are microalbuminuria followed by proteinuria. Proteinuria, when coupled with increased blood pressure, can result in ESRD. About 30% to 40% of those receiving a diagnosis of type 1 DM will develop ESRD (Reference 17). The incidence of developing ESRD in children and adolescents having a diagnosis of type 2 DM remains unknown. However, studies have shown that children and adolescents with diagnoses of type 2 DM have higher rates of microalbuminuria and earlier onset of diabetic nephropathy than those with diagnoses of type 1 DM (Reference 18). Risk factors for the progression of renal disease include poor metabolic control, smoking, and hypertension. Additional risk factors reported in those with type 1 DM include a family history of hypertension or cardiovascular disease. For patients with type 1 DM, annual screening for microalbuminuria is recommended beginning at age 10 years or in patients with a history of diabetes for 5 years. More frequent testing is required if microalbumin levels are elevated (Reference 9). For type 2 DM, it is recommended to screen for microalbuminuria from the time of diagnosis and then yearly thereafter (Reference 8). In patients with microalbuminuria, treatment with an angiotensin-converting enzyme inhibitor is suggested. In addition, any concomitant hypertension or hyperlipidemia should be treated.

Neuropathy

Peripheral and autonomic neuropathies, a complication of DM in adults, are not commonly seen in pediatric patients. Peripheral neuropathies are associated with pain, burning, and diminished sensation to filament testing (Reference 16). With time, peripheral neuropathies result in a loss of motor function (Reference 19). Children and adolescents suffering from peripheral neuropathies have persistent ongoing pain. Autonomic neuropathies include the cardiovascular, gastrointestinal, and genitourinary systems (Reference 20). Clinical presentation can include postural hypotension, gastroparesis, neurogenic bladder, impotence, and hypoglycemic unawareness. In rare instances, sudden death has been associated with abnormal heart rate responses and prolonged QT intervals (References 19, 20). Increased disease duration, particularly with poor metabolic control, is associated with earlier onset of neuropathies. Currently, the American Diabetes Association recommends foot examinations for all children with type 1 DM beginning at puberty and then yearly thereafter (Reference 9). It is also important to provide patient education on proper footwear and regular monitoring of feet. Although no recommendations exist for children and adolescents with type 2 DM, annual testing from the time of diagnosis and patient education should be considered.

Macrovascular Complications

Macrovascular complications of diabetes include cardiovascular, cerebrovascular, and peripheral vascular disease caused by atherosclerosis. Although these complications are rare in pediatric patients with DM, identifying and modifying the risk factors are important. Risk factors for atherosclerosis include hyperlipidemia, smoking, hypertension, obesity, and a family history of cardiovascular disease (Reference 9). A fasting lipid panel in children with type 1 DM older than 2 years up to puberty after 2 years of diagnosis is recommended. The test is to be repeated every 5 years if the low-density lipoprotein cholesterol is less than 100 mg/dL. For pubertal children and adolescents with type 1 DM, a lipid panel should be obtained at diagnosis and subsequently every 3–5 years if the low-density lipoprotein is less than 100 mg/dL (References 9, 21). For children and adolescents with type 2 DM, annual lipid profiles are recommended (Reference 22). Pharmacologic treatment is recommended for children older than 10 years if the low-density lipoprotein cholesterol is greater than 130 mg/dL (Reference 21).

Therapy Goals

The Diabetes Control and Complications Trial showed a decrease in microvascular complications in patients with type 1 DM when treated with intensive insulin therapy to maintain blood glucose (BG) as close to normal physiologic values as possible (Reference 23). In the trial, adolescents randomized to intensive treatment achieved lower glycosylated hemoglobin percentages, although unable to achieve glycosylated hemoglobin levels as low as the adults enrolled in the study (Reference 23). Despite being unable to achieve glycosylated hemoglobin levels less than 7%, adolescents in the

intensive treatment group had decreases in the onset of retinopathy or improvements in existing retinopathies, improved conduction velocities, and modest improvements in low-density lipoprotein cholesterol levels compared with those in conventional treatment (Reference 23). Long-term outcomes for those enrolled in the trial found that the continuation of intensive therapy (despite not achieving normal glycosylated hemoglobin levels) provided benefits, such as non-progression to proliferative retinopathy (Reference 24). However, an intensive insulin regimen predisposes an individual to increased weight gain and an increased number of hypoglycemic episodes. As mentioned previously, younger children are more vulnerable to hypoglycemia. Therefore, the American Diabetes Association has developed age-specific glycemic goals to balance the benefits and risks of tight glycemic control. Age-specific goals are listed in Table 2. Glycemic goals are higher for younger children because of the greater risk of hypoglycemia and low risk of long-term complications (Reference 9).

Glycemic goals for patients with type 2 DM more closely resemble goals for adult patients with DM. Goals for fasting BG are less than 126 mg/dL. In addition, the target for glycosylated hemoglobin is less than 7% (Reference 8).

In all pediatric patients with DM, attainment of normal growth and weight, prevention of acute and chronic complications, and minimization of adverse effects secondary to medications are desired.

Nonpharmacologic Therapy

Limited data exist on specific nutrition recommendations for children and adolescents with DM. Nutrition recommendations should be aimed at normal growth and development, attainment of glycemic goals, and management or prevention of comorbid conditions such as hypertension or hyperlipidemia (References 8, 9).

Children and adolescents with diagnoses of type 1 DM are typically underweight, whereas those presenting with type 2 DM tend to be overweight. However, in both groups, attaining a normal body weight is important. At this time, specific nutritional requirements for pediatric patients with either type 1 or 2 DM are unavailable; therefore, dietitians specializing in DM provide medical nutrition therapy by helping patients develop healthy eating habits as recommended by the U.S. Department of Agriculture. Height, weight, body mass index, and nutrition assessment should be conducted at least yearly (References 8, 9).

Medical nutrition therapy must consider specific insulin regimens prescribed to the patient. Initially, a consistent carbohydrate content for all meals and snacks is recommended, particularly for those on a fixed insulin regimen. However, this provides a challenge because of the erratic eating habits in this population. Some toddlers and young children may refuse to eat some or all of a meal, leaving them prone to hypoglycemia if insulin has been administered. In children with unreliable eating habits, the caregiver can administer rapid-acting insulin with the first bite of a meal. Adolescents also provide a challenge in eating appropriate (i.e., healthy) foods at regular intervals. In these instances, it is crucial for the patient and caregiver to count carbohydrate content in meals. Once a patient and caregiver are able to count carbohydrate content to adjust insulin doses, meals and snacks can be more flexible with respect to carbohydrate content. Other considerations in developing meal plans include increasing the consumption of carbohydrates (in the form of fruits, vegetables, and grains) and fiber and establishing a regular meal pattern because these factors have been shown to improve glycemic control in children and adolescents with type 1 DM (Reference 25).

Children and adolescents with DM benefit from regular exercise. In type 1 DM, adolescents who exercised regularly had an improved sense of well-being, quality of life, body composition, blood pressure, and lipid profiles (References 26, 27). Moderate physical activity for 30–60 minutes/day is recommended for children and adolescents with type 1 DM (Reference 9). However, exercise can increase the risk of hypoglycemia, necessitating a decrease in the insulin dose. For children and adolescents with type 2 DM, increasing physical activity as tolerated and minimizing sedentary behaviors are recommended. Exercise in this population can improve insulin resistance (Reference 8).

Table 2. Age-Specific Glycemic Goals for Type 1 Diabetes Mellitus (Reference 9)

	Plasma Blood Glucose Goal Range (mg/dL)		
Age (years)	Before Meals	Bedtime/Overnight	Glycosylated Hemoglobin
< 6	100–180	110–200	Between 7.5% and 8.5%
6–12	90–180	100–180	< 8%
13–19	90–130	90–150	< 7.5%

Pharmacologic Therapy

Because type 1 DM is a result of insulin deficiency, exogenous administration of insulin is required for the patient's survival. Although oral agents are typically used in type 2 DM, insulin is often necessary to achieve glycemic control.

Insulin

Insulin is a protein composed of 51 amino acids naturally produced by the pancreas. It is made up of two chains, alpha and beta, which are connected with disulfide bonds. Although porcine and bovine insulin were initially used, insulin products on the market today are manufactured from recombinant DNA technology (using human insulin) and then modified to various insulin analogs. Modifications in the structure allow alterations in the onset, peak, and duration of action of insulin as illustrated in Table 3. Because of pharmacokinetic differences, combinations of different types of insulin are used to mimic the normal physiologic release of insulin. For example, rapid- or short-acting insulin is used with meals to mimic pancreatic release in response to food, whereas long-acting insulin is used to provide basal insulin coverage throughout the day.

Efficacy of Insulin in Pediatric Patients

To date, no studies have reported increased efficacy of one form of insulin over another. Many forms of insulin have been studied in pediatric patients and have been shown efficacious. Table 4 lists advantages and disadvantages of specific insulin types in pediatric patients.

Dosing

The total daily dose of insulin depends on several factors including age, weight, pubertal status, diabetes duration, diet, exercise, BG, and concomitant illnesses (Reference 29). Dosing guidelines for various populations are listed in Table 5. Insulin dosing decreases during the "honeymoon phase." The honeymoon phase occurs after the initial onset of type 1 DM in which the pancreas increases insulin production before complete cessation of insulin secretion. The honeymoon phase begins several weeks after the diagnosis of type 1 DM and can last from several months to a year (Reference 28). During puberty, insulin requirements increase because of insulin resistance secondary to elevated growth and sex hormone secretion (Reference 9).

The total daily dose of insulin can be divided by various methods depending on the ability and needs of the patient and caregiver. Factors dictating which insulin regimen to use include the age of the child or adolescent, dietary patterns, exercise patterns, and school attendance (Reference 29). Types of regimens include split/mixed, basal/bolus, and administration by an insulin pump.

Split/Mixed Regimen

The split/mixed regimen consists of two or three daily injections of a standard insulin dose given as a combination of intermediate- or long-acting insulin and rapid- or short-acting insulin. Below is one common method of calculating the exact insulin doses for a patient using two daily injections:

1. Calculate the total daily dose for a patient. For example, a postpubescent adolescent weighing 60 kg would require 1 unit of insulin per kilogram (as indicated in Table 5) or 60 units of insulin per day.
2. Of the total daily dose, two-thirds of the insulin is administered in the morning and one-third in the afternoon/evening. In the example, the 60 units of insulin per day would be divided into 40 units in the morning and 20 units in the afternoon/evening.

Table 3. Insulin Types and Pharmacokinetic Parameters (References 28–30)

		Pharmacokinetics		
Insulin Type	**Brand (Generic) Names**	**Onset of Action**	**Peak of Action**	**Duration of Action (hours)**
Rapid-acting	NovoLog (aspart insulin) Humalog (lispro insulin) Apidra (glulisine insulin)	10–15 minutes	30–90 minutes	3–4
Short-acting	Novolin-R (regular insulin) Humulin-R (regular insulin)	30–60 minutes	2–4 hours	4–6
Intermediate-acting	Novolin-N (NPH insulin) Humulin-N (NPH insulin)	1–2 hours	3–10 hours	8–15
Long-acting	Lantus (insulin glargine)	2–4 hours	No peak	20–24
Long-acting	Levemir (insulin detemir)	1–2 hours	6–12 hours	6–24

Table 4. Advantages and Disadvantages of Insulin Types in Pediatric Patients

Insulin Type	Advantages	Disadvantages
Rapid-acting	Can be given with meals or immediately after meals (useful for toddlers with variable eating patterns) Treats hyperglycemia faster than regular insulin Can be used in CSII	Expensive
Short-acting	Abundant studies available Inexpensive	Must be given 30 minutes before meal Child may experience hypoglycemia with incomplete meals
Intermediate-acting	Can be mixed with other insulin without modification of pharmacokinetic parameters	Compared with long-acting insulin, may require more daily injections
Long-acting	Less intra-patient variability compared with intermediate-acting insulin Fewer hypoglycemia episodes compared with intermediate-acting insulin Greater satisfaction in adolescents compared with intermediate-acting insulin Less weight gain with insulin detemir compared with intermediate-acting insulin	Expensive Glargine may cause a burning sensation upon administration because of acidic pH

CSII = continuous subcutaneous insulin infusion.

Table 5. Recommended Insulin Dosage for Pediatric Patients (References 9, 29)

Stage/Type of Diabetes Mellitus Diagnosis	Recommended Total Daily Dose
Initial diagnosis	0.5–1 unit/kg/day
Honeymoon phase	< 0.5 unit/kg/day
Prepubertal children (out of honeymoon phase)	0.5–1unit/kg/day
Pubertal adolescents	May require up to 1.5 units/kg/day
Type 2 diabetes mellitus initial dosing (basal)	0.15-0.2 units/kg/day
Type 2 diabetes mellitus	May require up to 2 units/kg/day

3. When intermediate-acting insulin is used, the total amount of insulin is divided into two-thirds intermediate- and one-third rapid- or short-acting insulin. In the morning, 26 and 13 units of intermediate- and short-acting insulin, respectively, will be given. The afternoon/evening dose would be 13 and 7 units of intermediate- and short-acting insulin, respectively.
4. If long-acting insulin is administered, the dose is given as one-half long-acting and one-half short-acting insulin divided into AM and PM doses. The morning dose would be 30 units of long-acting insulin and 15 units of short-acting insulin. The evening dose would be 15 units of short-acting insulin. (Of note, if the patient is stabilized on an intermediate-acting insulin and is being converted to glargine, the dose of glargine must be decreased by 20% to prevent hypoglycemia. The dose need not be decreased if switching to detemir.)

The split/mixed regimen provides basal insulin coverage with the intermediate- or long-acting insulin and coverage of meals with the rapid- or short-acting insulin. This insulin therapy requires the patient to eat at regularly scheduled times and eat a consistent amount of carbohydrates per meal. Additional snacks may also be required to avoid hypoglycemic events, particularly if short-acting insulin is used. The use of intermediate-acting insulin may increase the frequency of nocturnal hypoglycemia. In some cases, replacing the intermediate-acting insulin with long-acting insulin decreases episodes of nocturnal hypoglycemia. The split/mixed regimen is typically not adequate in most patients to achieve desired glycosylated hemoglobin (Reference 9). Although administering insulin in this manner is ideal upon diagnosis of DM, after the honeymoon phase, it is recommended to move pediatric patients to a basal/bolus regimen (Reference 9).

Basal/Bolus Regimen

The basal/bolus regimen more closely resembles normal physiologic release of insulin than the split/mixed regimen. Long-acting insulin is administered to emulate normal physiologic basal insulin secretion, whereas pre-prandial insulin mimics pancreatic secretion in response to meals. Pre-prandial doses of insulin depend on the BG level before the meal, the anticipated amount of carbohydrates in the meal, and the expected amount of physical activity in subsequent hours (Reference 9).

In the basal/bolus regimen, one-half of the total daily insulin dose is administered as the basal insulin. The most commonly used basal insulin is glargine. Administration at bedtime is common; however, if nocturnal hypoglycemia is experienced, administration of glargine at dinner or breakfast is preferred. The other one-half of the total daily dose of insulin is divided between meals and snacks. The amount of insulin administered before each meal is calculated by estimating the insulin required to cover the carbohydrates eaten (determined by the carbohydrate factor and the insulin-to-carbohydrate ratio) and to correct a BG outside the goal range (determined by the correction factor). Although the basal/bolus regimen increases the daily number of injections, it has been associated with lower glucose concentrations and a lower incidence of nocturnal hypoglycemia.

The number of grams of carbohydrates consumed in a meal is calculated with the carbohydrate factor. Carbohydrate factors are available online at the U.S. Department of Agriculture Web site, or they can be calculated for prepackaged foods using the nutrition facts label. Once the carbohydrate factor is known, it is multiplied by the weight of the food (in grams) to determine the total amount of carbohydrates. Below is an example of how to calculate the number of grams in a particular food.

> A banana has a carbohydrate factor of 0.23 (meaning 23% of the banana is carbohydrate).
>
> If the banana weighs 120 g, it has 27.6 g of carbohydrates.

The insulin-to-carbohydrate ratio is the amount of insulin required per gram of carbohydrate in a meal. Typically, the ratio is 10–15 g of carbohydrates per unit of insulin, but it varies per patient and throughout the day. The insulin-to-carbohydrate ratio is calculated by dividing the total number of carbohydrate grams per day by the total daily dose of insulin. Typically, prepubescent children require less insulin per gram of carbohydrate, whereas pubertal adolescents require more (Reference 30). For example, if the total daily dose of insulin is 30 units and the child consumes 450 g of carbohydrates per day, the insulin-to-carbohydrate ratio is 15. This means that 1 unit of insulin is required for every 15 g of carbohydrates consumed. If this child ate the banana mentioned above, 1.8 units of insulin would be necessary to cover the carbohydrates in the banana.

The correction factor is the amount an individual's BG will decrease with 1 unit of insulin. The correction factor is calculated using the 1800 rule (for those using rapid-acting insulin as the bolus insulin). To estimate how much the BG will decrease per unit of insulin, 1800 is divided by the total daily dose (e.g., if the total daily dose is 20 units, the correction factor will be 90). A correction factor of 90 requires 1 unit of insulin for every 90 BG points above goal. For patients using short-acting insulin as the bolus insulin, 1500 should be used in place of 1800. With the basal/bolus regimen, the patient and caregiver must keep daily food logs, understand how to read nutrition facts labels, and monitor BG frequently.

Continuous Subcutaneous Insulin Infusion

The continuous subcutaneous insulin infusion (CSII) offers patients the benefit of a basal/bolus regimen without the need for several daily injections. The CSII provides a continuous infusion of insulin, and boluses are programmed with meals. In addition, the continuous infusion can be stopped during exercise to prevent hypoglycemic episodes. A recent study comparing different insulin regimens found that children and adolescents using an insulin pump had the lowest glycosylated hemoglobin compared with those using other regimens (Reference 31). In addition, there were fewer emergency department visits and hospitalizations. The CSII also decreases the incidence of hypoglycemic episodes (Reference 32). Other advantages and disadvantages of the CSII are listed in Table 6. Before a child or adolescent begins CSII therapy, the patient and caregiver must be motivated and understand the benefits and limitations of the CSII. At the very least, the patient and caregiver ought to be testing BG at least four times/day and be able to count carbohydrates. They should also be able to administer insulin by injections in case of pump malfunction (Reference 32).

Administration

Insulin is administered subcutaneously into the abdomen, front or lateral thigh, buttocks, or lateral aspect of the arm. In younger children with a small amount of fat, the upper outer quadrant of the buttocks is the preferred site of injection. Typically, insulin injected into the abdomen will absorb faster than insulin injected into the thigh (Reference 29). Injection in the

Table 6. Advantages and Disadvantages of Continuous Subcutaneous Insulin Infusion (References 29, 32)

Advantages	Disadvantages
Allows flexible dosing regimens	Larger needles inserted for pump
Decreases the amount of daily injections	Placement of pump may be difficult because of size
Small doses of insulin can be administered.	Dislodgment and risk of infection
Allows several boluses throughout meals	Costly
Families can download information regarding insulin doses.	
Increased patient and family satisfaction	
"Smart pumps" can automatically calculate meal or correction boluses.	

arm is not recommended in children because of the small amount of subcutaneous fat. This increases the chance of injecting the insulin intramuscularly instead of subcutaneously. Disinfecting the area is not necessary.

When mixing insulin to administer, it is important to instruct the patient or caregiver to draw up the regular insulin (clear) in the syringe before the intermediate-acting insulin (cloudy) to prevent contamination of the short-acting insulin. Although the manufacturer recommends not mixing glargine with any insulin, one study evaluated BG and glycosylated hemoglobin after the administration of glargine mixed with either lispro or aspart (Reference 33). Although the stability of the mixture remains unknown, if it is administered immediately after mixing, there are no differences between BG or glycosylated hemoglobin compared with being administered separately. Mixing insulin minimizes the number of injections administered to the child or adolescent.

Adverse Drug Reactions

Adverse drug reactions associated with insulin include injection-related reactions, hypoglycemia, hypokalemia, and weight gain. Injection-related reactions include local hypersensitivity reactions, lipohypertrophy, lipoatrophy, pain, insulin leakage, and bruising or bleeding (Reference 29).

Hypoglycemia is the most common and serious adverse reaction of insulin in children and adolescents. Hypoglycemia occurs more frequently in younger children and adolescents, those with low glycosylated hemoglobin (i.e., less than 8%), those with a history of severe hypoglycemia, and those who use higher insulin doses (References 9, 10). Common signs and symptoms of hypoglycemia include tremor, tachycardia, diaphoresis, pallor, impaired vision, dizziness, difficulty concentrating, slurred speech, irritability, inconsolable crying, headache, nausea, and seizures. Nocturnal hypoglycemia can lack symptoms or present with nightmares, restless sleep, or confusion upon awakening. Patients who have repeated episodes of hypoglycemia or a long duration of diabetes may develop hypoglycemic unawareness. Hypoglycemic unawareness results from the lack of counterregulatory hormones responding to low BG, specifically the lack of an adrenergic response. In these instances, the patient and caregiver must monitor BG more frequently. In addition, it may be necessary to decrease insulin doses to prevent hypoglycemia.

Hypoglycemia is categorized into mild, moderate, and severe hypoglycemia, although specific BG levels have not been defined for each category. Descriptions of each category of hypoglycemia and recommendations for management are listed in Table 7.

Caregivers (and teachers if the child is in school) should be counseled on how to recognize and treat hypoglycemia. In addition, it is necessary to explain when hypoglycemia is more likely to occur, such as during changes in insulin therapy, alterations in diet, increased physical activity, lower glycosylated hemoglobin levels, and after alcohol ingestion (Reference 10).

Table 7. Categories and Treatment of Hypoglycemia in Children and Adolescents (Reference 9)

Category	Symptoms	Management
Mild	Sweating Pallor Palpitations Tremors	10–15 g easily absorbable carbohydrate, such as juice
Moderate	Aggressiveness Drowsiness Confusion	20–30 g of glucose administered by another person
Severe	Altered state of consciousness Coma Seizure	30 mcg/kg (maximum 1 mg) subcutaneous glucagon

Drug Interactions

Several drugs increase or decrease the hypoglycemic effects of insulin as listed in Table 8. In addition, the signs of hypoglycemia can be masked with the concomitant use of a nonselective β-blocker. If a β-blocker is required, a cardioselective β-blocker (e.g., atenolol) should be considered.

Oral Antihyperglycemic Agents

Oral antihyperglycemic agents are indicated for the management of type 2 DM. Currently, only one medication, metformin, is approved for use in pediatrics. However, other oral agents have been studied. Table 9 summarizes the medications, available pediatric dosages, adverse drug reactions, and drug interactions of these medications.

Biguanides

Metformin (Glucophage) was studied in 10- to 16-year-old children and adolescents with new-onset type 2 DM in a double-blind, placebo-controlled trial for 16 weeks. Compared with placebo, those in the metformin treatment group had improved fasting BG and glycosylated hemoglobin, and they were more likely to meet at least one of the American Diabetes Association glycemic target levels (Reference 35). Subjects taking metformin had improvements in serum cholesterol concentrations compared with those on placebo. Metformin also resulted in weight loss, which is usually indicated in children and adolescents with type 2 DM.

Advantages of treatment with metformin are its proven efficacy (decreases glycosylated hemoglobin by 1% to 2%), generic availability, positive impact on weight and serum lipid concentrations, and relative safety (References 41, 42). Initially, metformin may cause gastrointestinal disturbances, including diarrhea. To minimize this adverse drug reaction, the medication is titrated to the maximal dose slowly, preferably over 3–4 weeks, and administered with food. Although the risk of lactic acidosis is low, metformin is contraindicated in children and adolescents with renal dysfunction or any condition that might predispose them to poor tissue perfusion such as alcohol abuse, radiographic studies with contrast, or surgery with general anesthesia (Reference 36). Metformin is considered first line in the treatment of type 2 DM in children and adolescents.

Table 8. Drug Interactions with Insulin (Reference 34)

Increases the Effect of Hypoglycemia	Decreases the Effect of Hypoglycemia
ACE inhibitors	Acetazolamide
Alcohol (acute use)	Alcohol (chronic use)
α-Blockers	Antiretrovirals
Anabolic steroids	Asparaginases
β-Blockers	Calcitonin
Calcium	Corticosteroids
Fluoxetine	Cyclophosphamide
Lithium	Diltiazem
MAO inhibitors	Dobutamine
Mebendazole	Epinephrine
Metformin	Isoniazid
Octreotide	Lithium
Pentamidine	Morphine
Pramlintide	Niacin
Pyridoxine	Nicotine
Sulfonamides	Oral contraceptives
Sulfonylureas	Phenytoin
Tetracyclines	Somatropin
Thiazolidinedione	Thiazide diuretics
	Thyroid hormone

ACE = angiotensin-converting enzyme; MAO = monoamine oxidase.

Thiazolidinediones

Rosiglitazone (Avandia) was compared with metformin in an 8-week, double-blind, controlled, parallel-group trial (Reference 37). The investigators found no difference between rosiglitazone and metformin with respect to lowering glycosylated hemoglobin. In June 2012, the results of a large, randomized, placebo-controlled trial evaluating the role of monotherapy (metformin) versus combination therapy (metformin and rosiglitazone) were published. The study enrolled patients 10–17 years of age having a diagnosis of type 2 DM for less than 2 years. The participants were initially treated with metformin until glycemic control was obtained. Then, the participants were randomized to metformin (1000 mg twice daily) monotherapy, metformin with lifestyle intervention (i.e., family-focused weight-loss behavioral changes including diet and exercise), or metformin with rosiglitazone (4 mg twice daily). Those who continued on metformin monotherapy experienced treatment failure 50% of the time, whereas participants treated with metformin and rosiglitazone had significantly lower treatment failures (39%). Those randomized to metformin monotherapy with lifestyle intervention had higher treatment failures (47%) than those on combination therapy. Common adverse effects reported in this study included gastrointestinal disturbances, infection, myalgia, elevation of liver enzymes (metformin), and mild hypoglycemia (metformin and rosiglitazone). One case of nonfatal lactic acidosis was

Table 9. Oral Antihyperglycemic Medications (References 35–40)

Medication	Drug Class/ Mechanism of Action	Dose	Contraindications	Adverse Drug Reactions	Drug Interactions
Metformin (Glucophage)	Biguanide: decreases hepatic production of glucose, decreases absorption of glucose in the gastrointestinal tract, and improves insulin sensitivity by increasing peripheral uptake of glucose.	10–16 years of age: 500 mg BID with meals, may titrate by 500 mg weekly to a maximal dose of 2,000 mg/day in divided doses	Renal disease or dysfunction (SCr ≥ 1.5 in males and ≥ 1.4 in females) Hypersensitivity to metformin Acute or chronic metabolic acidosis (including DKA)	Diarrhea Nausea/vomiting Flatulence Asthenia Indigestion Abdominal discomfort Headache Lactic acidosis	Alcohol Iodinated IV contrast
Rosiglitazone (Avandia)	Thiazolidinedione: agonist for the PPAR-γ; binding to the PPAR-γ improves insulin sensitivity in the peripheral tissues.	10–17 years of age: 2 mg twice daily titrated to a maximal dose of 8 mg/day after 8–12 weeks	Heart failure	Weight gain Edema Hepatotoxicity	Drugs that inhibit CYP2C8 may increase rosiglitazone concentrations, whereas inducers may decrease rosiglitazone concentrations.
Pioglitazone (Actos)	Thiazolidinedione: agonist for the PPAR-γ; binding to the PPAR-γ improves insulin sensitivity in the peripheral tissues.	Adult dose: 15 mg daily titrated to a maximal dose of 45 mg after 8–12 weeks as monotherapy and 30 mg if used with combination therapy	Heart failure Hypersensitivity to pioglitazone	Weight gain Edema Hepatotoxicity	Drugs that inhibit CYP2C8 may increase concentrations of pioglitazone, whereas inducers may decrease concentrations of pioglitazone; if coadministered with a strong inhibitor, the maximal dose of pioglitazone should be 15 mg/day.
Glimepiride (Micronase)	Sulfonylurea: enhances insulin secretion from the pancreas	8–17 years of age: 1 mg/day, titrated every 2 weeks by doubling the dose to a maximum of 8 mg/day taken 15 minutes before a meal	Hypersensitivity to glimepiride or sulfonamides	Hypoglycemia Weight gain Nausea/vomiting Photosensitivity	Highly protein bound drugs may increase the hypoglycemic effects of sulfonylureas.

BID = twice daily; CYP = cytochrome P450; DKA = diabetic ketoacidosis; IV = intravenous; PPAR-γ = peroxisome proliferator-activated receptor gamma; SCr = serum creatinine.

reported in the metformin monotherapy group. Those in the metformin and rosiglitazone arm had a slight increase in body mass index throughout the study. No long-term adverse effects on bone density were reported. Given the results of the study, rosiglitazone may be a viable adjunctive therapy in those who fail to respond to metformin monotherapy.

The short-term safety of pioglitazone (Actos) in adolescents was evaluated in a single- and multidose pharmacokinetic study (Reference 39). Adverse drug reactions reported in the study included nausea, diarrhea, headache, hypoglycemia, increased glutamyltransferase, and peripheral edema. Efficacy and long-term safety were not established.

A potential advantage of thiazolidinediones is preserving pancreatic beta-cell function (Reference 43). One major disadvantage for this population is the weight gain associated with the thiazolidinediones. The thiazolidinediones have a class black box warning on the relationship between the onset and worsening of congestive heart failure in adults. In addition, in adults, the thiazolidinediones have been associated with hepatotoxicity and bone fractures. Because of the lack of efficacy data in pediatric patients and the associated adverse effects with the thiazolidinediones, rosiglitazone and pioglitazone are not recommended as first-line therapy in type 2 DM at this time.

Sulfonylureas

Glimepiride (Amaryl) has been studied in children and adolescents between 8 and 17 years of age in a 24-week, randomized, single-blind, parallel-group trial with metformin as the control (Reference 40). Both groups had significant decreases in glycosylated hemoglobin from baseline. Participants taking glimepiride had slight increases in serum cholesterol, low-density lipoprotein, triglycerides, and weight. No differences were reported in adverse drug reactions between the two treatment groups. Adverse reactions included hypoglycemia, abdominal pain, diarrhea, nausea, and headache. Glimepiride may be useful as adjunctive therapy to metformin in children and adolescents not wanting to use insulin. Disadvantages include the risk of hypoglycemia and weight gain. No other sulfonylureas have been studied in children. Glipizide and glyburide do not have any pediatric dosing, efficacy, or safety information.

Meglitinides

Meglitinides are considered short-acting insulin secretagogues. Compared with sulfonylureas, they have a more rapid onset and shorter duration of action. Because of their shorter duration of action, these medications must be taken with meals. This could be advantageous for children and adolescents who do not eat at regularly scheduled times. Nateglinide (Starlix) and repaglinide (Prandin) are two medications in this drug class. These medications have not been evaluated for use in the pediatric population.

Glucosidase Inhibitors

Glucosidase inhibitors inhibit the α-glucosidase enzyme located in the small intestine, resulting in the inhibition of breakdown and absorption of glucose and other monosaccharides. A common adverse reaction with this class of medications is flatulence, which may be unacceptable to adolescents. Drugs in this class include acarbose (Precose) and miglitol (Glyset). These medications have not been evaluated for use in the pediatric population.

Approach to Pharmacotherapy in the Pediatric Patient with Type 1 DM

Children and adolescents with diagnoses of type 1 DM require immediate treatment with insulin. If the patient presents with DKA, intravenous administration is the preferred route. Once the patient is stabilized, they may be transitioned to a split/mixed regimen to allow the patient and caregiver to become familiar with injecting insulin. During the honeymoon phase, the split/mixed regimen or the use of intermediate- or long-acting insulin alone is typically adequate for glycemic control (Reference 29). After the honeymoon period, a split/mixed regimen can be reinstituted, or the patient can begin to move toward a basal/bolus regimen.

Special Considerations in Pediatric Patients with Type 1 DM

Sick Day Management

Children and adolescents are prone to hypoglycemia, hyperglycemia, ketosis, and DKA during times of illness. Consulting with the medical team and careful monitoring of hydration status, BG, and urine ketones is necessary.

Illness can cause an increase or decrease in insulin requirements; however, it is imperative to continue insulin administration during an illness. Discontinuing insulin during an illness predisposes a child or adolescent to DKA (Reference 44). At a minimum, basal insulin should be continued even if dose requirements are less (Reference 28). Lack of appetite, diarrhea, or nausea and vomiting contribute to hypoglycemia with continued insulin therapy. If the child or adolescent is unable to tolerate or eat solid foods, sugar-containing foods and drinks (e.g., soda, juice, ice pops) can be given to avoid hypoglycemia. If the child or adolescent is unable to tolerate such foods and drinks, glucagon administration is warranted (Reference 9). Because glucagon is associated with nausea and vomiting, a smaller dose of 10 mcg per year of age is typically administered (Reference 45).

Increased levels of stress hormones during an illness precipitate hyperglycemia and insulin resistance, thus increasing insulin requirements. Ketones can develop, despite euglycemia, in response to low glucose availability for intracellular metabolism. For this reason, monitoring of BG and urine ketones is necessary to determine whether the administration of more insulin is needed. Often, smaller doses of insulin are administered more frequently such as 5% to 10% or 10% to 20% (if ketones are present) of the total daily insulin dose every 3–4 hours (Reference 28). Hydration is especially important to aid in the diuresis of glucose and ketoacids.

School Administration

Because children and adolescents spend a large part of their day in school or day care, it is important to educate school nurses and teachers about diabetes, monitoring BG, administering insulin, and recognizing the signs, symptoms, and treatment of hypoglycemia. A child or adolescent with diabetes can participate fully in school activities.

Adolescents and Adherence

Adolescence becomes a difficult time for glycemic control for several reasons. The onset of puberty increases growth and sex hormones, resulting in increased insulin resistance. In addition, some adolescents seek more independence, may become rebellious, or may experiment with alcohol or illicit substances, which can result in nonadherence to diabetes management.

Adolescents with type 1 DM are at increased risk of psychiatric and behavioral disorders compared with adolescents without type 1 DM. Eating disorders, such as bulimia nervosa and binge eating disorder, occur in up to 30% of adolescents with type 1 DM, with females being affected more than males (References 46, 47). Teenagers may also resort to excessive exercise, laxative use, or omission of insulin in an attempt to lose weight (Reference 47). Other disorders seen commonly in this population include depression, anxiety, impulsivity, hyperactivity, and aggression (References 48, 49). Ongoing screening for such psychiatric disorders is recommended.

Approach to Pharmacotherapy in the Pediatric Patient with Type 2 DM

Initial treatment of type 2 DM in a child or adolescent depends on the clinical presentation at diagnosis. Insulin therapy may be necessary to achieve glycemic control initially, particularly if the child or adolescent presents with a glycosylated hemoglobin greater than 9%, symptomatic hyperglycemia, HHS, or DKA. Once stabilized, an oral antihyperglycemic agent, such as metformin, can be initiated and insulin discontinued. Lifestyle intervention (i.e., diet, exercise) should also be incorporated into treatment.

Lifestyle intervention for a 3- to 6-month period before initiating pharmacologic therapy is an option for a patient who is asymptomatic or has a glycosylated hemoglobin between 7% and 9% at diagnosis. Adding an oral antihyperglycemic agent is considered either at the end of the 3- to 6-month trial of lifestyle modification or at diagnosis. Failure to reach a therapeutic glycosylated hemoglobin goal after 3–6 months of therapy typically necessitates the addition of a second oral antihyperglycemic agent or insulin. Initially, a basal insulin can be administered once daily. If therapeutic goals are still not achieved, the addition of rapid- or short-acting insulin with meals may be warranted. A small retrospective study evaluating various treatment regimens in type 2 DM reported few patients were able to attain therapeutic goals with monotherapy (Reference 50). However, further studies are necessary to determine optimal combination therapy.

Monitoring Pharmacotherapy

Monitoring Therapeutic Outcomes

Glycemic control in DM is monitored with glycosylated hemoglobin and BG. Glycosylated hemoglobin represents glycemic control during a 3-month period. Therefore, it is monitored every 3 months in both type 1 and 2 DM. Self-monitoring of blood glucose (SMBG) by the patient or the caregiver is performed daily to monitor trends in BG and to adjust insulin doses or food intake. Self-monitoring of blood glucose is ideally performed pre- and post-prandially, nocturnally, during dose adjustments of medications, during illness, or when symptoms of hyper- or hypoglycemia are present (References 9, 22). In type 1 DM, at least four tests per day are necessary including before breakfast and dinner, before bedtime, and nocturnally (e.g., between 3:00 AM and 4:00 AM). The frequency in type 2 DM may be less often. In those with hypoglycemic unawareness, during periods of increased activity or illness, more frequent testing is warranted. In type 1 DM, monitoring of urine glucose and ketones is indicated when BG is greater than 250 mg/dL or during an acute illness to detect early ketosis and subsequent DKA (Reference 28).

Nocturnal monitoring is necessary to differentiate the dawn phenomenon and Somogyi effect when fasting hyperglycemia occurs in the morning. The dawn phenomenon is a result of normal BG increases in the early morning because of increases in growth hormone, increased hepatic glucose production, and increased insulin resistance (Reference 29). The Somogyi effect is a rebound hyperglycemia caused by a hypoglycemic event during the night. Management of the dawn phenomenon and Somogyi effect is provided in Table 10.

Self-monitoring of blood glucose allows adjustments in insulin doses and self-management of diabetes by the patient and caregiver. For a patient on a basal/bolus regimen, preprandial SMBG (and carbohydrate content of the meal) dictates the amount of insulin to be administered before a meal. Table 10 provides insulin adjustment recommendations for some situations of hyper- or hypoglycemia.

Monitoring Toxicities Associated with Pharmacotherapy

While on insulin therapy, patients and caregivers must be counseled on recognizing the signs, and treatment, of hypoglycemia. Hypoglycemia is also detected with SMBG. In addition, patients and caregivers should monitor injection sites for local adverse effects including allergic reactions, lipoatrophy, and lipohypertrophy.

Table 10. Insulin Adjustments for Hypo- and Hyperglycemia in Children and Adolescents

Deviation	Adjustment	Precautions
Elevated fasting BG before breakfast (dawn phenomenon)[a]	(1) Increase the PM dose of intermediate- or long-acting insulin. OR (2) Administer the PM dose of intermediate-acting insulin later.	Obtain BG at 3–4 AM to ensure nocturnal hypoglycemia does not occur.
Elevated fasting BG before breakfast (Somogyi effect)[a]	(1) Decrease the PM dose of intermediate- or long-acting insulin.	
Elevated BG after meal	(1) Increase the rapid- or short-acting insulin administered before meals.	Evaluate the carbohydrate content of the meal to ensure it is appropriate.
Elevated BG before lunch/dinner	(1) Increase the AM basal insulin dose (if using intermediate-acting insulin). OR (2) Increase the prebreakfast rapid- or short-acting insulin dose.	

[a]Must differentiate between dawn phenomenon and Somogyi effect.
AM = morning; BG = blood glucose; PM = nightly.

Renal and hepatic function and a complete blood cell count are usually obtained before initiating metformin and then yearly. Metformin alone does not cause hypoglycemia; however, BG monitoring is necessary to assess efficacy. Although lactic acidosis is rare, it is important to monitor for conditions that may predispose the patient to a hypoxic state.

Hepatic function should be evaluated before initiating a thiazolidinedione. If liver enzymes are elevated, the underlying liver disease is treated, or the thiazolidinedione is not used (Reference 51). Monitoring of hepatic function is recommended periodically throughout treatment with a thiazolidinedione. Because of an increased risk of fractures, it is necessary to monitor bone health in pediatric patients and supplement with calcium or vitamin D when indicated. When used as monotherapy, thiazolidinediones do not cause hypoglycemia. However, in combination with insulin or an insulin secretagogue, the risk of hypoglycemia increases. It is not recommended to use rosiglitazone in combination with insulin (Reference 51).

Sulfonylureas can cause hypoglycemia; therefore, patients must be educated about the signs and treatment of hypoglycemia. Patients with G6PD (glucose-6-phosphate dehydrogenase) deficiency are at increased risk of hemolytic anemia if treated with a sulfonylurea (Reference 52). An alternative treatment (e.g., metformin, insulin) is indicated in this population. Other hematologic reactions, such as agranulocytosis, thrombocytopenia, and pancytopenia, are rare. No specific laboratory monitoring is indicated unless an adverse reaction is suspected.

Future Pharmacotherapy/ Adjunctive Pharmacotherapy

Three classes of medications are currently approved for adults as adjunctive treatment of DM, amylin analogs, glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase IV (DPP-IV) inhibitors. None is currently approved in pediatrics.

Amylin Analogs

Pramlintide (Symlin), an amylin analog, is approved as adjunctive therapy in adults with either type 1 or 2 DM on mealtime insulin not achieving glycemic control (Reference 53). Amylin is naturally secreted by the beta cells of the pancreas with insulin in response to food. It is reported to enhance the action of insulin by decreasing glucagon production, slowing gastric emptying, decreasing hepatic glucose production, and increasing satiety (Reference 54). Pramlintide, which is administered subcutaneously before meals, mainly decreases postprandial hyperglycemia. The most common adverse drug reactions include nausea, vomiting, and anorexia. Pramlintide alone does not cause hypoglycemia; however, hypoglycemia can occur (and is

listed as a black box warning) when used in combination with insulin, and concomitant use may require dose adjustments of the insulin. Weight loss has been associated with pramlintide use.

Short-term pilot studies have been conducted in children and adolescents with type 1 DM (References 55–57). Pramlintide may be beneficial in decreasing postprandial hyperglycemia, glycosylated hemoglobin, weight, and insulin doses. Pramlintide appears to be well tolerated, with nausea being the most common adverse drug reaction. There were no reports of hypoglycemia.

Incretin Mimetics

Exenatide (Byetta), a GLP-1 receptor agonist, is approved for use in adults with type 2 DM. Glucagon-like peptide-1 is an incretin secreted by intestinal L-cells in response to food ingestion (Reference 54). Incretins enhance insulin release from the pancreas in response to elevated BG, inhibit glucagon release after meals, decrease gastric emptying, and increase satiety (Reference 58). Exenatide is administered subcutaneously before meals. The most common adverse effects are nausea, hypoglycemia (particularly when used in combination with a sulfonylurea), vomiting, diarrhea, dizziness, headache, and dyspepsia (Reference 59). Exenatide has been associated with fatal pancreatitis in adults. Exenatide improves postprandial BG, glycosylated hemoglobin, and weight in adults (Reference 59).

Exenatide pharmacokinetics have been evaluated in adolescents with type 1 and 2 DM and are comparable to those in adults (References 58, 60). In both studies, postprandial BG decreased with the administration of exenatide. Exenatide was well tolerated with no reports of hypoglycemia.

DPP-IV Enzyme Inhibitors

Dipeptidyl peptidase IV enzyme inhibitors, which include sitagliptin, vildagliptin, alogliptin, and saxagliptin, are oral agents approved for use in adults with type 2 DM. The DPP-IV inhibitors block the enzyme responsible for GLP-1 degradation, resulting in increased activity of GLP-1. These agents decrease glycosylated hemoglobin as well as fasting and postprandial BG. The agents, however, are not associated with weight loss. The DDP-IV inhibitors are well tolerated (Reference 61). No data in pediatrics are currently available.

Diabetic Ketoacidosis

Diabetic ketoacidosis is a life-threatening acute complication of DM. It is characterized by hyperglycemia, severe dehydration, electrolyte losses from the intra- and extracellular fluid compartments, and acidosis. It results from absolute insulin deficiency, whether from undiagnosed DM, nonadherence to insulin therapy, insulin pump malfunction, illness, infection (particularly gastrointestinal illness with nausea and vomiting), stress, or trauma.

Pathophysiology of DKA

The lack of circulating insulin results in hyperglycemia caused by the inability to uptake glucose into peripheral tissue or into glycogen storage. It also stimulates the release of counterregulatory hormones including glucagon, catecholamines, cortisol, and growth hormone. These hormones further increase serum glucose levels because of increased glycogenolysis and gluconeogenesis. The hyperglycemia results in serum hyperosmolarity and an osmotic diuresis. The osmotic diuresis results in dehydration, electrolyte loss, and decreased glomerular filtration rates. The lack of insulin also results in increased lipolysis, leading to the release of free fatty acids and subsequent production of ketones, particularly β-hydroxybutyric and acetoacetic acids. The ketones, together with lactic acidosis from poor tissue perfusion, result in a metabolic acidosis. Until exogenous insulin is administered, the counterregulatory hormones continue to be released, resulting in further hyperglycemia and ketone production (Reference 62).

Presenting Signs and Symptoms

Common presenting signs and symptoms of DKA include dehydration, polyuria, polydipsia, recent weight loss, rapid, deep sighing (Kussmaul respiration), and fruity-smelling breath. Changes in mental status, such as decreased alertness or loss of consciousness, can also be present. Other nonspecific symptoms, such as nausea, vomiting, or fever, may indicate the presence of an infection that could have precipitated DKA (Reference 12). The physical examination typically includes an evaluation of hydration status, vital signs (cardiovascular and respiratory), and neurologic status. Laboratory tests include BG, blood or urine ketones, electrolytes (including sodium, potassium, calcium, phosphorus, bicarbonate, and blood urea nitrogen), blood gases, serum osmolarity, and a urinalysis for ketone detection (Reference 63). If available, blood levels of β-hydroxybutyrate are measured. Because of potassium abnormalities that occur, an electrocardiogram is obtained (Reference 12).

Diagnosis of DKA

The diagnostic criteria for DKA are listed below (Reference 12):

1. BG greater than 200 mg/dL
2. Venous pH less than 7.3 or bicarbonate less than 15 mmol/L
3. Ketonemia or ketonuria

The severity of DKA is classified into mild, moderate, and severe depending on the serum pH. A pH between 7.2 and 7.3 is mild, between 7.1 and 7.2 is moderate, and less than 7.1 is severe DKA (Reference 62).

Therapy Goals

The therapy goals in the management of DKA include the following (Reference 12):

1. Correction of dehydration
2. Correction of acidosis and reversal of ketosis
3. Decreased BG levels
4. Correction of electrolyte abnormalities
5. Prevention of DKA complications

Treatment of DKA

Treatment of Dehydration

The initial goal of rehydration in DKA is reperfusion of organs, not complete restoration of fluid lost. For that reason, on initial presentation, a fluid bolus of 10–20 mL/kg over 1–2 hours with either 0.9% saline or lactated Ringer's is recommended. The bolus may be repeated if necessary, but not to exceed 40 mL/kg of total intravenous fluid within the first 4 hours of treatment (Reference 63). After the initial boluses, administration of the estimated fluid deficit is given over a 48-hour period to prevent cerebral edema. The total fluid deficit can be difficult to estimate; therefore, administering 1.5–2 times the daily maintenance fluid requirements is not exceeded (Reference 63). The tonicity of the replacement fluid should be at least 0.45% saline. If the serum sodium levels are low, 0.9% saline is recommended, whereas if the sodium levels are high, 0.45% saline is preferred (Reference 64).

Correction of Acidosis and Ketosis Reversal

The initiation of insulin not only decreases BG but also, more importantly, suppresses lipolysis and ketogenesis, which will reverse the ketoacidosis. Insulin therapy is started 1–2 hours after the initiation of the fluid boluses to minimize the risk of cerebral edema (Reference 62). Regular insulin administered intravenously is the preferred insulin and route of administration. The initial insulin dose is 0.1 unit/kg/hour until the serum pH is greater than 7.3, the bicarbonate is greater than 15 mmol/L, or the anion gap is no longer present. Because BG normalization can occur before the ketoacidosis resolution, dextrose 5% is added to the intravenous fluids once the BG level falls below 300 mg/dL to prevent hypoglycemia (Reference 12). If the BG falls rapidly, dextrose 10% or 12.5% is used in place of the 5%. In children and adolescents sensitive to insulin, the insulin dose is decreased to 0.05 unit/kg/hour. Despite BG correction, the insulin is continued until the ketoacidosis is resolved. Once the ketoacidosis is resolved, the patient can be transitioned to a subcutaneous form of insulin. Bicarbonate is not generally recommended for the treatment of DKA (Reference 12).

Correction of Electrolyte Abnormalities

Although serum potassium levels can appear normal in a child or adolescent with DKA, total body potassium is typically low. Increased levels of serum potassium result from the extracellular shift of potassium secondary to acidosis and hypertonicity. Conversely, at presentation, low serum potassium levels are because of increased elimination caused by osmotic diuresis. In addition, on administration of insulin, serum potassium levels decrease because of the shift of potassium into the cells. Regardless, potassium replacement begins early in the treatment of DKA. If the potassium level is elevated at presentation, adequate renal output is established before initiating potassium replacement (Reference 65). The potassium is generally replaced as potassium chloride, acetate, or phosphate at 40 mEq/L. Potassium acetate or phosphate are preferred over potassium chloride to avoid hyperchloremic metabolic acidosis (Reference 64). However, if potassium phosphate is administered, it is limited to no more than one-half the total potassium replacement required (Reference 63).

Sodium and phosphate may be decreased in DKA. Sodium is typically replaced with the intravenous fluids administered for rehydration. Phosphate can be replaced when potassium phosphate is used to treat hypokalemia; however, unless the phosphate level is less than 1 mg/dL and the patient is experiencing muscle weakness, it is not recommended to replace phosphate (Reference 62).

Monitoring of Therapy

During the treatment of DKA, intensive monitoring is necessary. If possible, vital signs, neurologic status, fluid input and urine output, and capillary BG should be monitored hourly (Reference 12). Electrolytes and blood gases are monitored every 2–4 hours, whereas blood urea nitrogen, creatinine, and hematocrit can be obtained every 6–8 hours. Anion gap and serum osmolality should also be monitored with each laboratory draw.

Children and adolescents with DKA must be closely monitored for signs of cerebral edema. These signs include headache, vomiting, increasing blood pressure, decreasing heart rate, decreasing oxygen saturation, and changes in neurologic status such as confusion and lethargy. Computed tomography may assist in the diagnosis of cerebral edema; however, evidence of cerebral edema is not always present on imaging studies (Reference 12). The onset of cerebral edema is typically within 4–12 hours after the treatment initiation for DKA.

Conclusions

It has been estimated that a child given a diagnosis of diabetes at age 10 in the year 2000 will live 20 years less than a child not receiving a diagnosis of DM at the same age (Reference 66). In addition, the quality of life for these children will be less than for those without DM. However, because of advances in pharmacologic therapy, such as insulin analogs, improvements in metabolic control in DM can prolong both the quantity and quality of life for pediatric patients afflicted with DM. Such care requires full participation of the caregiver and patient, when possible, with a multidisciplinary health care team to optimize pharmacotherapy (and minimize adverse reactions) to prevent complications.

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PART V

Neurology/Psychiatry

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Section Editor

CHAPTER 25

Cerebral Palsy

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Learning Objectives

1. List underlying causes and risk factors for cerebral palsy (CP).
2. Discuss initial and ongoing assessment of the patient with CP.
3. Recognize and recommend treatment options for generalized and localized spasticity.
4. Discuss nonpharmacologic and pharmacologic treatment options for drooling.
5. Describe the role of pamidronate in the treatment of low bone mineral density associated with CP.

Abbreviations in This Chapter

AAN	American Academy of Neurology
BMD	Bone mineral density
CNS	Child Neurology Society
CP	Cerebral palsy
c-PVL	Cystic periventricular leukomalacia
CSF	Cerebrospinal fluid
EPNS	European Paediatric Neurology Society
GABA	γ-Aminobutyric acid
GMFCS	Gross Motor Function Classification System
ODT	Orally disintegrating tablet
UCP	United Cerebral Palsy

Introduction

In 2004, an International Workshop on Definition and Classification of Cerebral Palsy was convened in Bethesda, Maryland. Participants emphasized the importance of viewing cerebral palsy (CP) as a clinical descriptive term and defined CP as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior, by epilepsy, and by secondary musculoskeletal problems. (Reference 1)

Although CP results from a nonprogressive disturbance, the symptoms in patients change with time. This changing clinical course necessitates frequent assessment by health care providers to ensure that treatments are continually evaluated and adjusted to optimize overall function. As drug treatment options expand for motor disorders and other accompanying conditions, pharmacists play an increasing role in selecting optimal medication choices for patients with CP.

Epidemiology and Classification

Cerebral palsy is the most common childhood physical disability. United Cerebral Palsy (UCP) is a nonprofit organization dedicated to providing education about CP and advocacy and support for patients and their families. The UCP estimates that 764,000 children and adults in the United States manifest at least one CP symptom (Reference 2). The average prevalence in the United States is estimated at 3.3 per 1,000 for children 8 years of age (Reference 3).

Because CP covers a broad range of clinical presentations, the disorder is classified on the basis of motor abnormalities, accompanying impairments, anatomic and neuroimaging findings, causation, and timing (Reference 1). Patients may present with more than one movement abnormality, but it is recommended that they be classified by the dominant type: spasticity, dystonia, choreoathetosis, or ataxia (Reference 1). Around 81% of children have spastic CP (Reference 3). Functional motor abilities in individuals with CP are most often described using the Gross Motor Function Classification System (GMFCS) (Reference 4). The GMFCS has five levels of classification and is determined from self-initiated movement with an emphasis on sitting, transfer, and mobility. Table 1 defines the levels of classification for the GMFCS and estimates the percentage of children with CP who function at each level. The GMFCS may be used in the consideration of treatment options.

Accompanying impairments in patients with CP may interfere with the activities of daily living to an equal or greater extent than characteristic motor disabilities. Epilepsy is present in 35% of children with CP (Reference 3), and it can complicate treatment choices by increasing the risk of drug-drug interactions between

Table 1. GMFCS Levels and Estimates of Children Who Function at Each Level

Level	General Description[a]	8-Year-Old Children Who Function at Level (%)[b]
I	Walks without restrictions: limitations in more advanced gross motor skills	38.1
II	Walks without assistive devices: limitations walking outdoors and in the community	16.4
III	Walks with assistive mobility devices: limitations walking outdoors and in the community	13.2
IV	Self-mobility with limitations: children are transported or use power mobility outdoors and in the community	15.2
V	Self-mobility is severely limited even with the use of assistive technology.	17.1

[a]Information from Reference 4.
[b]Information from Reference 3.
GMFCS = Gross Motor Function Classification System.

therapies for the movement disorder and seizure control. Constipation and urinary incontinence are other frequently seen conditions that require concurrent drug therapies. Additional impairments include hearing and vision abnormalities, intellectual disabilities, emotional and behavioral disorders, and musculoskeletal problems.

Classification by anatomic and neuroimaging findings currently emphasizes the importance of assessing CP involvement in all body regions and using imaging technology as it develops. At present, it is difficult to categorize by causality; however, as mechanisms of injury in fetal and infant brain development become better understood, classification by cause may have greater utility. Categorization by timing of insult is only recommended when there is reasonably definitive evidence of the cause (Reference 1).

Etiology and Risk Factors

Because CP occurs because of an injury or disturbance in the developing fetal or infant brain, etiology and risk factors are often described as prenatal, perinatal, or postnatal (References 5, 6). It is estimated that 70% to 80% of CP cases are acquired prenatally, often from unknown causes (References 6, 7). Birth complications, including intrapartum asphyxia, account for a small percentage, or 5% to 10%, of cases (Reference 7). Box 1 lists prenatal and perinatal risk factors associated with an increased risk of CP. The relationship between prematurity and CP is complicated by evolving neonatal intensive care practices. Cystic periventricular leukomalacia (c-PVL) and severe intraventricular hemorrhage are independent risk factors for CP in premature patients, and decreased incidence of CP has been attributed to decreasing c-PVL (Reference 8). Fewer patients acquire CP from postnatal causes occurring in infancy, including bacterial meningitis, viral encephalitis, or a brain injury from a motor vehicle collision, a fall, or child abuse (Reference 7). Prevention of postnatal causes is a promising strategy for decreasing the prevalence of CP (Reference 5).

Clinical Presentation and Diagnosis

Initial Assessment and Diagnosis

Most children with CP present as infants and toddlers, and diagnosis often occurs by 2 years of age. In patients with milder symptoms, CP may not be confirmed before 4–5 years of age. Early, careful assessments of motor development, muscle tone, and risk factors are key aspects of diagnosis. A delay in reaching motor developmental milestones is usually viewed as a classic sign of CP in at-risk patients. However, some milestones, such as hand preference and even rolling over in select patients, may be achieved before typical ages. Box 2 lists early clinical features of CP. The differential diagnosis often focuses on eliminating disorders that are progressive, including metabolic or genetic disorders or central nervous system tumors. Targeted laboratory testing may help rule out these processes (Reference 7).

Box 1. Prenatal and perinatal factors associated with an increased risk of cerebral palsy.[a]

- Preterm birth
- Lower gestational age
- Lower birth weight (particularly VLBW, ELBW)
- Neonatal encephalopathy
- Multiple pregnancy
- Assisted reproductive technology
- Intrauterine infection and inflammation
- Genetics

[a]Adapted from Reference 5.
ELBW = extremely low birth weight (less than 1,000 g).
VLBW = very low birth weight (1,000 g to less than 1,500 g).

Neuroimaging techniques may be helpful in distinguishing CP from other movement disorders and potentially identifying the location of injury in CP. Neuroimaging is often performed in the perinatal period if there is a history of prematurity or birth complications. In patients who present at a later age, neuroimaging is recommended if the etiology has not been identified (Reference 9). Magnetic resonance imaging is preferred to computed axial tomography because it results in a greater suggestion of the etiology and timing of insult that led to CP (Reference 9). In patients with unilateral (hemiplegic) CP, neuroimaging is helpful to evaluate for unexplained cerebral infarction, and in these patients, laboratory testing to evaluate for coagulopathies should be considered (Reference 9).

Continuing Assessment of Muscle Tone, Movement, and Associated Conditions

Evaluation of muscle tone and movement is important for patients with CP to determine which motor abnormalities may be present. Symptoms related to motor dysfunction vary greatly from person to person and may be isolated or mixed. Box 2 lists symptom examples on the basis of motor abnormality type. Spasticity, the most common abnormality, describes a form of hypertonia, which is characterized by a velocity-dependent resistance of a muscle to stretch (Reference 10). Dyskinesia describes a movement pattern that is involuntary, uncontrolled, recurring, and occasionally stereotypical (Reference 11). Dyskinetic CP is termed *dystonic* if movements are stiff with increased tone and *choreoathetotic* if movements are slow and writhing with decreased tone (Reference 11). Ataxia in CP describes a loss of orderly muscle contraction with movements that are performed with abnormal force, rhythm, and accuracy (Reference 11).

The motor abnormalities of CP may make it more difficult to recognize other, concurrent impairments. Although epilepsy, intellectual disabilities, and speech and language disorders are not always present, patients should be screened for them (Reference 9). For epilepsy assessment, electroencephalography should be obtained if the child exhibits any features that suggest a seizure disorder (Reference 9). Hearing and vision evaluations may require referral to specialists because some children are unable to cooperate and complete typical screenings.

In addition, nutrition, growth, and other problems with swallowing function should be monitored (Reference 9). An early sign of feeding difficulties is poor weight gain. In some infants, the difficulty may be caused by the delayed development of oral motor

Box 2. Clinical features of cerebral palsy.

- Early clinical features[a]
  - Slow to reach motor developmental milestones (examples: roll over, sit, crawl, smile, or walk)
  - Hypotonia (floppy) or hypertonia (stiff, rigid)
  - Unusual posture
  - Persistence of the Moro reflex after 6 months
  - Favoring of one side of the body or development of hand preference earlier than 12 months
- Clinical symptoms related to motor abnormalities[b]
  - Spasticity
    - Stiff or tight muscles
    - Increased deep tendon reflexes
    - Scissored gait with toe-walking
    - May be unilateral (one body side) or bilateral (both body sides)
    - Upper or lower extremities may be more affected.
  - Dyskinesia
    - Slow, uncontrollable writhing movements
    - Grimacing or drooling caused by hyperactive muscles of the face and tongue
  - Ataxia
    - Unsteady wide-based gait
    - Intention tremor
    - Difficulty with precise motions, such as writing or buttoning a shirt

[a]Adapted from References 6 and 7.
[b]Adapted from Reference 7.

skills related to prematurity. The inability to control secretions can make feeding challenging and place the patient at risk of aspiration. Patients with feeding difficulties are often initially evaluated by assessing their swallowing function with a modified barium swallow study; then, diet modifications are made on the basis of the results obtained. Failure to thrive is common in children with moderate to severe CP. In these children, providing enteral nutrition through a gastrostomy tube is an option to improve nutritional status (Reference 7). When gastrostomy tubes are present, oral medications are often given through the tube. Liquid drug formulations should be used when available for this route of administration. If a tablet preparation is used by crushing and mixing with water, care should be taken to ensure this will not alter drug properties or cause a physical blockage of the gastrostomy tube (see the Parenteral and Enteral Nutrition chapter). Poor nutrition and altered growth also affect skeletal development and are contributing factors to the low bone mineral density (BMD) seen in patients with CP, especially in nonambulatory children with moderate to severe motor impairment (References 12, 13).

The use of outcome measures that help clinicians quantify and monitor function is a valuable aspect of CP assessment. The GMFCS (Reference 4) is fundamental in evaluating motor functional abilities in children 1–18 years of age with CP, and its use has increased as a clinical and research tool (Reference 14). The GMFCS and other instruments that measure outcomes in patients with CP are available on the CanChild Centre for Childhood Disability Research Web site (Reference 15). In patients with spasticity, determining the degree of spasticity is helpful in evaluating response to therapy. The Ashworth (Reference 16), the modified Ashworth (Reference 17), and the modified Tardieu scales (Reference 18) are three instruments used to grade levels of spasticity. The modified Tardieu scale may be more effective in quantifying a change in spasticity than the modified Ashworth scale (Reference 18).

Treatment

The overall treatment goals for patients with CP are to improve function and aesthetics, capabilities, and quality of life. Early, intensive treatment optimizes clinical outcomes (Reference 7). Care plans are individualized and comprehensive. They incorporate several components including physical and behavioral therapy, drug therapy, surgery, and mechanical aids. Drug therapy is focused on managing spasticity and other issues related to the motor aspects of the disorder. Supportive care concerns (e.g., low BMD) also benefit from pharmacotherapy.

Spasticity

Specific treatment objectives for spasticity are to maximize active function, ease caregiving, relieve pain, and decrease or prevent contractures (Reference 19). First, patients should be assessed for muscle weakness and strength. If weakness is present, it is important to determine whether spasticity is actually helping with function (e.g., with weight bearing or a caregiver's ability to transfer) (References 19, 20). In these patients, treatments should be carefully monitored for worsening weakness and counterproductive effects on function. Second, nonspastic causes of pain and poor positioning should be resolved before other treatments (Reference 20). Once these are addressed, nonpharmacologic management through physical therapy or orthotics is optimized. Regular stretching exercises of affected limbs are prescribed to maintain range of motion and prevent contractures (Reference 19). Typically, caregivers are taught and encouraged to perform these exercises. For patients with unilateral spasticity, constraint-induced movement therapy is a rehabilitation option. For example, in a patient with unilateral upper extremity spasticity, the arm with the greater function is constrained to force the use of the lesser functioning arm (Reference 21). Ankle-foot orthoses are commonly used to maintain proper foot position and decrease the propensity to toe-walk (Reference 19).

After physical management is maximized, pharmacologic therapy for spasticity is considered. Treatment options include drugs for generalized or localized spasticity. Although not fully elucidated, many symptoms of spasticity result from an upper motor neuron lesion causing disinhibition of spinal reflexes or the failure of reciprocal inhibition (Reference 22). The drug effect is aimed at altering these abnormalities. Figure 1 illustrates the proposed mechanisms of action for the drugs most commonly used to treat generalized spasticity: oral clonazepam, diazepam, baclofen, tizanidine, dantrolene, and intrathecal baclofen. Botulinum toxin products, phenol, and alcohol are used for localized spasticity as denervation agents (Reference 19).

The choice of an antispastic drug is often based on experience and trial and error as opposed to evidence-based medicine, particularly with oral medications. The research with these agents is older, did not use outcome measures for function or rigorous study design, or was conducted primarily in an adult population (Reference 19). The Quality Standards Subcommittee of the American Academy of Neurology (AAN) and the Practice Committee of the Child Neurology Society (CNS) addressed these limitations in a practice parameter published in 2010 that evaluated the

evidence basis for antispasticity treatments in children and adolescents with CP (Reference 24). Table 2 summarizes their conclusions and recommendations regarding drug therapy for spasticity. Oral baclofen is extensively used in clinical practice to treat children with CP and spasticity despite the recommendation that the evidence is insufficient to support its use (Reference 24).

Diazepam and Clonazepam

Diazepam, a benzodiazepine, is the oldest treatment option for spasticity still in use today (Reference 25) and is probably effective for short-term management (Reference 24). Clonazepam is another benzodiazepine used as an antispastic agent. Their effects on spasticity are mediated through γ-aminobutyric acid (GABA), specifically by increasing the affinity of GABA for $GABA_A$ receptors, resulting in presynaptic inhibition and reduced monosynaptic and polysynaptic reflexes (Reference 25). Both diazepam and clonazepam also have anticonvulsant activity, which may provide added benefit in patients with an accompanying seizure disorder. Clonazepam, in particular, has indications as a treatment for absence seizures and myoclonus.

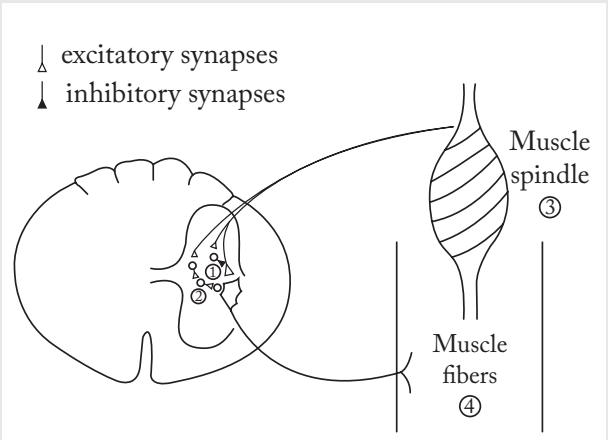


Figure 1. Presumed sites of action for drugs used to treat generalized spasticity.

(1) Clonazepam and diazepam facilitate GABA-A–mediated presynaptic inhibition; (2) baclofen inhibits activity of polysynaptic reflexes by GABA-B receptor activation; (3) tizanidine acts on α_2-adrenergic receptors; and (4) dantrolene reduces the sensitivity of peripheral intramuscular receptors and reduces release of calcium ions from the sarcoplasmic reticulum, which thus weakens muscle contraction.
GABA = γ-aminobutyric acid.
Reproduced from Dietz and Young (Reference 23) with permission.

Sedation is the most common, often dose-limiting, adverse effect of the benzodiazepines when they are used for spasticity (Reference 25). However, for patients with insomnia, the benzodiazepines may aid with sleep difficulties if dosed at night. Other adverse effects that limit long-term use include weakness, sialorrhea, and ataxia (Reference 24).

Diazepam and clonazepam are given orally or enterally for spasticity, and both have rapid oral absorption (Reference 26). They are considered long-acting benzodiazepines with elimination half-lives of up to 50 hours in adults and faster rates in children (Reference 26). Long-acting benzodiazepines are considered to have a decreased risk of withdrawal, but this is a known concern with both agents. Because of this risk, abrupt discontinuation should be avoided after prolonged use, and if possible, substitution with intravenous or rectal diazepam should be made if oral or enteral cessation becomes necessary (References 24, 25).

Dosage should be initiated at a low dose and titrated up for the benzodiazepines. The lowest effective maintenance dose should be given to minimize sedation. Diazepam is available in tablets, a solution, and a liquid concentrate for oral use. Clonazepam is available in tablets and a newer orally disintegrating tablet (ODT) formulation. Although the clonazepam ODTs have increased dosing and administration options for pediatric patients, it is sometimes necessary to use a compounded oral liquid (Reference 27). Table 3 lists doses and available products for diazepam and clonazepam.

Tizanidine

Tizanidine is a newer oral agent whose effectiveness for spasticity has been primarily shown in adults with multiple sclerosis or a spinal cord injury (Reference 25). Little information exists on its effectiveness for spasticity reduction in children with CP (Reference 24). As an α_2-adrenergic agonist, its ability to reduce muscle tone occurs through the hyperpolarization of motor neurons, with a subsequent decrease in excitability (References 25, 28, 29). It is also described as having antinociceptive effects mediated through substance P. This capability to reduce pain may be a contributory factor to its benefits on tone (Reference 25). Tizanidine is extensively metabolized in the liver. Cytochrome P450 (CYP) 1A2 is the primary enzyme for metabolism, and the potential for drug interactions should be assessed when it is given with other drugs metabolized through this pathway (Reference 30).

Sedation, hypotension, asthenia, dry mouth, dizziness, hallucinations, and hepatotoxicity have been reported as adverse effects in adults (Reference 24). Initiating tizanidine as a single daily dose at bedtime may minimize sedation effects on daily function. Dosage is then titrated upward by adding doses throughout the day. Titration may also help avoid nausea and vomiting in patients (Reference 25). A study found significant reduction in spasticity using the Ashworth scale in 10 children given tizanidine at a dosage of 0.05 mg/kg/day for 6 months versus 30 children who received placebo (Reference 31). Larger studies are needed to determine the optimal dosage in the pediatric population. Tizanidine is available as tablets and capsules. When tizanidine is given with food, the extent of absorption is increased for both tablets and capsules, but to a greater degree with the tablet formulation. Peak plasma concentrations and time to peak are also altered and differ (Reference 29). Pediatric dosing is limited as well by the lack of a commercial or extemporaneous liquid formulation, but it is possible to open the capsules and sprinkle the contents on applesauce. This administration method increases the peak and extent of absorption and decreases the time to peak concentration (Reference 30). Table 3 summarizes oral dose and formulation information for tizanidine.

Dantrolene

Dantrolene is unique among oral drugs used for spasticity, with a mechanism of action having direct effects on skeletal muscle. It acts by inhibiting the release of calcium at the sarcoplasmic reticulum, resulting in

Table 2. Evidence-Based Conclusions and Recommendations on Antispasticity Drug Therapy in Children and Adolescents with CP[a]

Drug	Conclusions	Recommendations
For Generalized Spasticity		
Baclofen (intrathecal)	Inadequate data on continuous intrathecal baclofen as antispasticity treatment; CSF leaks, seromas, catheter-related complications, and wound infections occur frequently and milder complications occur less often	Insufficient evidence to support or refute use for spasticity (U)[b]
Baclofen (oral)	Conflicting evidence regarding effectiveness to reduce spasticity and improve function; systemic toxicity is found in some patients	Insufficient evidence to support or refute use for spasticity or to improve motor function (U)
Dantrolene (oral)	Conflicting evidence regarding effectiveness to reduce spasticity; weakness, drowsiness, and irritability are frequent adverse effects.	Insufficient evidence to support or refute use for spasticity (U)
Diazepam (oral)	Probably effective short-term therapy for spasticity; improved motor function not addressed; ataxia and drowsiness were adverse effects in most studies.	Consider a short-term antispasticity treatment (B); insufficient evidence to support or refute use to improve motor function (U)
Tizanidine (oral)	Possibly effective spasticity treatment with no toxicity in one small study	May be considered for treatment of spasticity (C); insufficient evidence to support or refute use to improve motor function (U)
For Localized Spasticity[c]		
AbobotulinumtoxinA, OnabotulinumtoxinA	Effective treatment to reduce spasticity in upper and lower extremities; conflicting evidence on functional improvement; generally safe, but severe generalized weakness may occur.	For localized/segmental spasticity in upper or lower extremities with CP that warrant therapy, should be offered as generally safe treatment (A); insufficient evidence to support or refute use to improve motor function (U)

[a]Adapted from Reference 24, which includes clinical context summaries.
[b]Classification of recommendations: A = established effective for the given condition in the specified population (requires two or more class I studies), B = probably effective for the given condition in the specified population (requires one class I study or two consistent class II studies), C = possibly effective for the given condition in the specified population (requires one class II study or two consistent class III studies), U = data inadequate or conflicting and treatment is unproved given current knowledge.
[c]No publications met criteria for review of rimabotulinumtoxinB, phenol, and alcohol.
CP = cerebral palsy; CSF = cerebrospinal fluid.

Table 3. Doses and Formulations for Oral Antispasticity Drugs

Drug	Oral Dose	Formulations[a]
Benzodiazepines		
Clonazepam	*Infant and child (noted for seizure):*[b] Younger than 10 years or 30 kg: Initial: 0.01–0.03 mg/kg/day divided into two or three doses/day (maximum initial 0.05 mg/kg/day); increase by no more than 0.5 mg every third day Maintenance: 0.1–0.2 mg/kg/day divided into three doses/day (not to exceed 0.2 mg/kg/day) Older than 10 years (30 kg) or adult: Initial: not to exceed 0.5 mg tid; may increase by 0.5–1 mg every third day Maintenance: 0.05–0.2 mg/kg/day (not to exceed 20 mg/day)	0.5-, 1-, and 2-mg tablets 0.125-, 0.25-, 0.5-, 1-, and 2-mg ODT *Extemporaneous formulation:*[c] 0.1 mg/1 mL suspension
Diazepam	*Child:*[d] 0.05–0.1 mg/kg/day divided into two to four doses/day (maximum 0.8 mg/kg/day) *Adult:* 2–10 mg/day divided into two to four doses/day	2-, 5-, and 10-mg tablets 5 mg/5 mL oral solution 5 mg/1 mL oral concentrate
Miscellaneous		
Baclofen	*Child:* Younger than 2 years: Initial: 2.5 mg every 8 hours[d] Maintenance: 10–20 mg/day in divided doses[e] Maximum: 40 mg/day in divided doses[e] 2–7 years: Initial: 5 mg every 8 hours[d] Maintenance: 20–30 mg/day in divided doses[e] Maximum: 60 mg/day in divided doses[e] Older than 7 years: Initial: 5 mg every 8 hours[d] Maintenance: 30–40 mg/day in divided doses[e] Maximum: 200 mg/day in divided doses[e] Titrate dose at 7-day intervals to effective dose.[d] *Adult:*[b] Initial: 5 mg tid; increase 5 mg/dose every 3 days Maximum: 80 mg/day in divided doses	10- and 20-mg tablets *Extemporaneous formulations:*[c] 5 mg/mL; 10 mg/mL
Dantrolene	*Child:*[b] Initial 0.5 mg/kg/dose once daily for 7 days; then increase to 0.5 mg/kg/dose tid for 7 days; then increase to 1 mg/kg/dose tid for 7 days; then increase to 2 mg/kg/dose tid. (Do not exceed 400 mg/day.) *Adult:* Initial 25 mg once daily for 7 days; then increase to 25 mg tid for 7 days; then increase to 50 mg tid for 7 days; then increase to 100 mg tid. (Do not exceed 400 mg/day.) *Titrate dose to effect; if no benefit with increased dose, decrease to previous lower dose*	25-, 50-, and 100-mg capsules *Extemporaneous formulation:*[c] 5 mg/mL
Tizanidine	*Limited information available in pediatrics:* *Child to 15 years:*[f] 0.05 mg/kg/day Initial younger than 10 years: 1 mg/day given at bedtime[d] Initial older than 10 years: 2 mg/day given at bedtime[d] *Adult:*[g] Initial: 4 mg/day; gradually increase by 2–4 mg Doses may be given at 6- to 8-hour intervals (maximum three doses/day) Maximum: 12 mg/dose; 36 mg/day	2-, 4-, and 6-mg capsules 4-mg tablets

[a] Adapted from References 26, 30.
[b] Adapted from Reference 26.
[c] Complete directions for extemporaneous formulation in Reference 26.
[d] Adapted from Reference 28.
[e] Adapted from Reference 35.
[f] Adapted from Reference 31.
[g] Adapted from Reference 30.
ODT = orally disintegrating tablet; tid = three times/day

muscle weakness (Reference 19). Because of its peripheral mechanism, it may be a helpful agent in patients whose spasticity results from a traumatic brain injury. However, conflicting results on the effectiveness of dantrolene led the AAN and CNS practice parameter to conclude that evidence was insufficient to support or refute its use for spasticity in children with CP (Reference 24).

The use of dantrolene is also limited by its adverse effect profile. Although the therapeutic effects occur outside the central nervous system, it is often associated with dose-dependent, diffuse weakness (Reference 29). Drowsiness and irritability are additional common adverse effects in children with CP (Reference 24). Dantrolene is associated with hepatoxicity. In one series, the risk of fatal hepatic disease was increased in women older than 35 years, in patients receiving higher daily dosages, and in patients with a diagnosis of multiple sclerosis (Reference 32). Even though studies of dantrolene for spasticity in children with CP did not report hepatotoxicity (Reference 24), all children being initiated on therapy should undergo baseline and periodic liver function test monitoring. Dantrolene should be avoided if patients are receiving additional hepatotoxic therapies.

Dantrolene is extensively metabolized in the liver and has an active metabolite, 5-hydroxy dantrolene. It has potential for interactions with drugs metabolized through the CYP3A4 enzyme (Reference 26). Therapeutic benefit for spasticity may take several days for onset, and the dose is titrated to effect at 7-day intervals. When no advantage is seen with a dosage increase, the dose should be lowered to minimize toxicity (Reference 26). Dantrolene is commercially available in capsules that may be opened and mixed with juice or liquid. Extemporaneous oral liquids may be prepared, but these formulations are limited by their complexity in preparation or short time to expiration (Reference 33).

Baclofen

Baclofen is a GABA agonist used to treat spasticity by oral and intrathecal administration. Baclofen crosses the blood-brain barrier and binds to $GABA_B$ receptors in laminae I–IV of the spinal cord (Reference 34). It appears to block both monosynaptic and polysynaptic afferents (Reference 28). The mechanism may be as a direct inhibitory neurotransmitter or through hyperpolarization of afferent nerve terminals (Reference 28). Baclofen is rapidly absorbed after oral administration. It is partly metabolized by the liver, but a significant amount is eliminated unchanged by the kidneys (Reference 29).

Oral baclofen is often considered the drug of choice for adults with spasticity caused by spinal cord injury (Reference 19), and it is widely used as a treatment for spasticity in children with CP (Reference 24). Oral baclofen is associated with sedation and confusion, which may lessen after several weeks of therapy (Reference 19). Initiating baclofen at the lowest possible dose may minimize these adverse effects (Reference 24). Various oral dosing regimens have been published for baclofen, largely based on small trials and expert opinion (References 28, 34, 35). A study assessed oral baclofen dosing in a retrospective review of 86 pediatric patients with spasticity (Reference 35). The study found that higher dosage requirements were associated with longer time since the onset of injury responsible for spasticity, increasing age of patient, and number of concurrent antispasticity medicines (Reference 35). If oral baclofen is discontinued, a gradual wean is recommended because abrupt discontinuation may cause withdrawal symptoms including increased spasms, hallucinations, confusion, fever, and seizures (References 24, 25, 29). Oral baclofen is commercially available as tablets. It can be compounded into a liquid form (References 36, 37), but it may be preferable to prescribe by ½- or ¼-tablet doses for consistency (Reference 25). Table 3 provides oral dosing and formulation information for baclofen.

Intrathecal baclofen is administered through an implantable pump that provides a continuous or variable-rate infusion. The AAN and CNS practice parameter concluded that the use of continuous intrathecal baclofen for spasticity in children with CP was not supported by adequate data (Reference 24). A consensus statement from the European Paediatric Neurology Society (EPNS) reviewed the efficacy of the treatment and stated that a reduction in spasticity is best established in patients with severe spasticity in the lower limbs consistent with GMFCS levels IV–V (Reference 38). Decreased spasticity has also been shown in upper limbs, but to a lesser extent (Reference 38). In a study of 37 patients with CP, the authors found significant improvement in motor function, as assessed by the Gross Motor Function Measure (Reference 39). The best improvements were seen in patients younger than 18 years (Reference 39). Box 3 summarizes the EPNS recommendations for selecting patients to receive intrathecal baclofen. Although there are no limitations on patient weight to be considered a candidate for therapy, children should have large enough body

mass to allow implantation of the pump, which is about the size of a hockey puck (Reference 19). Some experts recommend a minimum of 15 kg of body weight (Reference 29). Figure 2 illustrates a child with a baclofen intrathecal pump.

Because the drug is delivered directly to the subarachnoid space around the spinal cord, the required dosage of intrathecal baclofen is less than 1% of an oral dose, which decreases sedation risk (Reference 19). Children and adults (mean age 16 years) administered intrathecal baclofen at doses of 70–1,395 mcg/day had cerebrospinal fluid (CSF) concentrations equal to 0.2–20 mcg/mL from an intrathecal catheter aspirate (Reference 40). These levels did not statistically correlate with dose but did compare with CSF concentrations of 12–96 mcg/mL in adults receiving oral dosages of 30–90 mg/day (Reference 41). In contrast, plasma concentrations of baclofen were at or below the limit of detection (10 ng/mL) in children receiving intrathecal dosages of 77–400 mcg/day in a separate study (Reference 42). In summary, the CSF concentrations achieved by reported doses of intrathecal baclofen are comparable to levels seen with oral therapy while the plasma concentrations are minimized.

Box 3. Summary of selection criteria for patients receiving intrathecal baclofen.

- Confirmed spasticity
  - Aggravating factors managed
  - Spasticity not optimally managed by physical therapies, oral baclofen, and other drugs, botulinum toxin injection
  - Spasticity interferes with patients' abilities and quality of life
- Ability and motivation to attend regular follow-up and monitoring
- Age older than 4 years
  - NB. Baclofen for intrathecal use (Lioresal) is licensed for use in children older than 4 years; though children younger than this have been treated, regulations on patient age vary from country to country.
- No limitations on patient weight, though overweight patients may need to lose weight before surgery

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NB = nota bene; note well.

Once selected for therapy, the patient and his or her caregivers should receive education on the treatment, its possible effects, potential complications, what will be required of them, and protocols for emergency management (References 34, 38). A screening intrathecal dose is often given as a single injection to assess patient response. The aim of the test is to show spasticity reduction in several muscle groups (Reference 34). It may also help determine an initial dose. However, it does not reliably predict functional improvement (Reference 38). Dosage titration is recommended when a patient initiates continuous intrathecal infusion to minimize adverse effects (Reference 38). Dosage usually increases slowly during the first year and then stabilizes (Reference 34). With time, the pump can be programmed to vary the infusion rate to accommodate

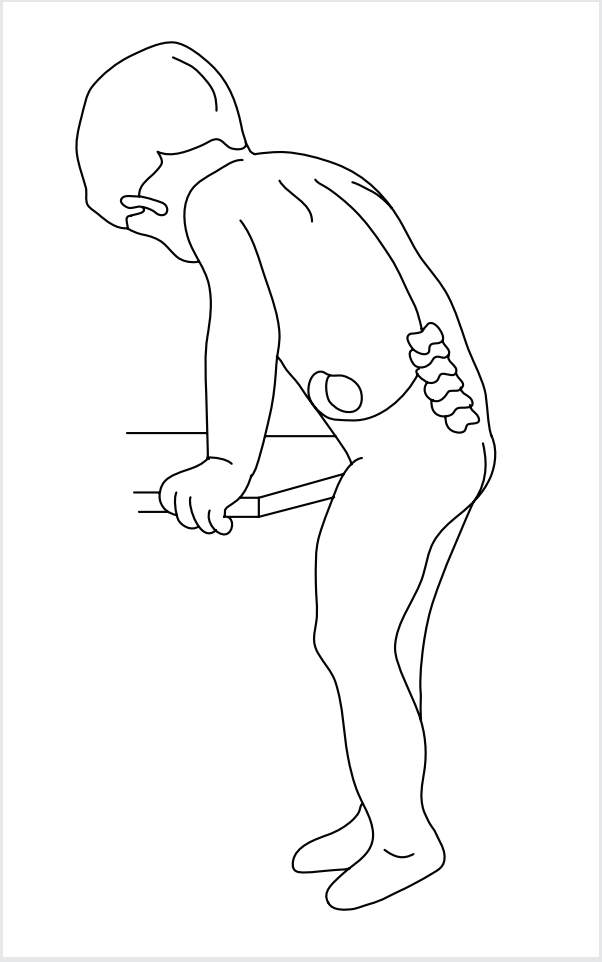


Figure 2. Child with an intrathecal baclofen pump.

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the patient's activities throughout the day (Reference 19). Patients with ventriculoperitoneal shunts may require lower doses (Reference 34). Box 4 provides dosing information for intrathecal baclofen.

Careful monitoring by health care professionals experienced with intrathecal baclofen and the infusion device is essential. Patients typically need to have the pump's reservoir transcutaneously refilled by their provider at 2- to 6-month intervals. Pump and battery function should be monitored, and the infusion device should be replaced before the battery expires (Reference 38).

Abrupt withdrawal after unexpected discontinuation and unintentional overdose are troublesome complications with intrathecal baclofen. Potential causes of discontinuation include an empty pump reservoir, a displaced or leaky catheter, or a programming or refill error (Reference 34). Withdrawal symptoms consist of elevated temperature, altered mental status, exaggerated rebound spasticity, and muscle rigidity (Reference 43). Severe itching, agitation, hallucinations, hypotension or labile blood pressure, and seizures have been reported (References 19, 34). Rarely, symptoms progress to rhabdomyolysis, multiple organ system failure, and death (Reference 43). Early recognition and reinstitution of therapy are essential to managing withdrawal. Benzodiazepines and life support may be needed (Reference 19).

Box 4. Intrathecal baclofen dosing.

Screening dose:
50 mcg (very small patients 25 mcg) intrathecally with observation for 4–8 hours

If initial response is less than desired, a second dose of 75 mcg intrathecally may be given after 24 hours with observation for 4–8 hours. If response still inadequate, a final dose of 100 mcg intrathecally may be given 24 hours later. If the patient is unresponsive to the 100-mcg dose, he or she is not a candidate for an implanted pump for infusion.

Initial total daily dose for infusion:
Double-screening dose that gave positive effect and administer over 24 hours

If the efficacy of the screening dose lasted greater than 8 hours, then the initial dose should be the screening dose administered over 24 hours.

Average daily dose:
12 years or younger: 100–300 mcg/day
Older than 12 years and adults: 300–800 mcg/day

Compiled from References 26 and 43.

Signs of intrathecal baclofen overdose include excessive hypotonia, drowsiness or decreased arousal, and respiratory depression (Reference 34). If toxicity is suspected, the patient should be taken to the hospital immediately for assessment and emptying of the pump reservoir. Overdose has generally been related to pump malfunction or dosing error (Reference 43). A careful appraisal of the device's programming is an important part of the evaluation. To lessen the risk of complications, patients should be educated on activities that may alter infusion flow. Examples are exposure to considerable changes in altitude or temperatures, excessive twitching or stretching, twiddling with the pump or catheter through the skin, and strong electromagnetic interference (Reference 44).

It is critical to monitor for infections associated with intrathecal baclofen therapy. Infections can occur in the pump area, or more rarely, meningitis can develop (Reference 24). In one survey, wound dehiscence with secondary infection, particularly in the first 2 months after implantation, was the most likely reason for pump removal (Reference 45). Children of small size, patients with a gastrostomy tube, or those unable to ambulate were at higher risk of wound complications (Reference 45).

Botulinum Toxin A

Botulinum toxin A is a commercially available denervation therapy given as an intramuscular injection to treat localized or segmental (unilateral or lower or upper extremity) spasticity (Reference 24). It is one of seven serotypes of exotoxin produced by *Clostridium botulinum,* the pathogen that causes botulism, an infectious disease characterized by a general paralysis (Reference 29). It acts as a denervation agent at the nerve terminal end plate by blocking acetylcholine release at the neuromuscular junction, a critical step in initiating a muscle response (References 34, 46). This results in a flaccid muscle paralysis and can provide a selective, reversible effect that can be used to balance forces across joints (Reference 46). Serotype B is available as a pharmaceutical product, but its clinical use is not as wide because of its shorter duration of muscle relaxation (Reference 34). In the United States, three preparations of botulinum toxin A and one preparation of botulinum toxin B are commercially available. In 2009, the U.S. Food and Drug Administration (FDA) issued a safety alert that included a recommendation to modify the established drug names of the botulinum toxin products to

emphasize their individual potencies and prevent medication errors (Reference 47). Table 4 lists the revised drug and trade names for botulinum toxins A and B and product availability.

Licensed use of botulinum toxin products for spasticity varies greatly between countries and is restricted to specific preparations, indications, and dose limits (Reference 48). In the United States, none of the products are currently labeled for treatment of spasticity in children, but onabotulinumtoxinA has an FDA-approved indication for treatment of upper limb spasticity in adults (Reference 49). The updated EPNS consensus statement on botulinum toxin for children with CP notes that, although unlicensed, individualized use on the basis of dose, dilution, indication, and muscle group(s) represents appropriate treatment when it is consistent with clinical experience (Reference 48). The AAN and CNS practice parameter recommends botulinum toxin A be offered as effective and generally safe therapy for localized or segmental spasticity in children with CP, but it notes conflicting evidence on functional improvement (Reference 24). It excludes botulinum toxin B from review because of insufficient published data (Reference 24). In a separate evidence-based review, the AAN recommends specific spasticity indications for botulinum neurotoxin injection for children with CP (Reference 50). The AAN recommends that injection of calf muscles be offered as treatment for equinus varus, a foot anomaly in which the heel turns inward, and the foot is plantar flexed. It should be considered a therapeutic option for adductor spasticity, pain control in children undergoing adductor-lengthening surgery, and upper extremity spasticity (Reference 50). The studies supporting these recommendations used onabotulinumtoxinA and abobotulinumtoxinA.

All botulinum toxin products are unique with respect to molecular structure, method used to determine biologic activity, pharmacokinetics, pharmacodynamics, and manufacturing process (References 34, 48). The products are not interchangeable, and fixed-dose conversion ratios are not applicable in the treatment of spasticity in children with CP (Reference 48). Dosage is individualized per patient. The EPNS recommends calculations be made for "(1) total units per treatment session, (2) total units per kg body weight per session, (3) units per muscle, (4) units per injection site, (5) units per kg body weight per muscle" (Reference 48). Table 5 lists patient factors to consider when dosing botulinum toxin products. The clinical effects of onabotulinumtoxinA and abobotulinumtoxinA typically last 3–4 months, necessitating repeat injections (Reference 24). Maintaining an interval of at least 3 months is recommended to lessen the risk of antibody development (Reference 51).

The most common adverse effects reported with the use of botulinum toxin A products in children with CP are pain at injection site, excessive weakness, unsteadiness and increased falls, and fatigue (Reference 24). Strategies

Table 4. Botulinum Toxin Preparations

Drug Name	Trade Name [Manufacturer]	Product Availability
AbobotulinumtoxinA	Dysport [Ipsen Biopharm]	300- and 500-unit vials
IncobotulinumtoxinA	Xeomin [Merz Pharmaceuticals]	50- and 100-unit vials
OnabotulinumtoxinA	Botox [Allergan]	100- and 200-unit vials
	Botox Cosmetic [Allergan]	50- and 100-unit vials
RimabotulinumtoxinB	Myobloc [Solstice Neurosciences]	2500-, 5000-, and 10,000-unit vials

Table 5. Factors to Consider When Dosing Botulinum Toxin Products for Spasticity in Children with Cerebral Palsy

Patient Factors	Muscle Factors
Age	Mass
Severity of CP	Number of muscles to be injected
Predominance of movement disorder	Target muscle strength
Degree of joint deformity	Activity of muscle
General health	Dynamic vs. fibrotic type
Accompanying impairments	Motor end plate distribution in muscle
Experience from previous injections	

CP = cerebral palsy.
Compiled from References 46 and 48.

to manage local pain at injection include topical anesthetics before injection, anxiolytics, or light sedation during injection (Reference 51). Accurate localization of muscles for injection is aided by electromyography, electrical stimulation, and ultrasonography. If botulinum toxin A is administered at the hip level, transient urinary and bowel incontinence is an additional adverse effect (Reference 34). The risk of this complication generally peaks 1 month after injection (Reference 34). Patients receiving aminoglycosides, other drugs that interfere with neuromuscular transmission, or muscle relaxants should be monitored closely for potentiation of effect of botulinum toxin (References 49, 52).

Systemic toxicity from the spread of botulinum toxin effects from the injection site has been reported. The 2009 FDA safety alert addressed this concern for pediatric and adult patients. For pediatrics, the postmarketing case reports were primarily related to use for spasticity in children with CP (Reference 53). Specifically, the FDA stated:

> The reported cases of spread of botulinum toxin effect from beyond the site injection were described as botulism, or involved symptoms including difficulty breathing, difficulty swallowing, muscular weakness, drooping eyelids, constipation, aspiration pneumonia, speech disorder, facial drooping, double vision, or respiratory depression. (Reference 53)

Cases involving ventilatory support and fatality were reported. On the basis of the postmarketing evaluation, the FDA recommended that health care professionals who use botulinum toxin products (1) recognize that dosage strength expressed in units is different between products and that doses expressed in units are not interchangeable between products; (2) be alert to and educate patients and caregivers about potential adverse effects because of the distant spread of botulinum toxin from the injection site; (3) understand that these adverse events have occurred as early as several hours and as late as several weeks after injection; and (4) advise patients to seek immediate medical attention if they develop any of these symptoms (Reference 53). The FDA safety alert has resulted in the revised names of products, labeling changes including a boxed warning, and the implementation of a Risk Evaluation and Mitigation Strategy with a Medication Guide for all products.

Additional Treatments

Phenol and alcohol are other injectable denervation agents used for localized spasticity. Their use is limited by complications of long-term pain or paresthesia and the need for expert technical skills for correct administration (Reference 51). The AAN and CNS practice parameter excluded them from review because of insufficient published data (Reference 24). For surgical options, orthopedic and neurosurgical procedures are available that may improve gait, contractures, hip alignment, and neuromuscular scoliosis.

Drooling

Drooling is involuntary loss of saliva from the mouth. Sialorrhea is often used as a synonym for drooling, referring to excessive flow of saliva. Sialorrhea may be caused by the overproduction of saliva. However, most patients with CP produce normal amounts of saliva but have difficulty managing it in the oral cavity (Reference 54). Drooling is described as anterior if the saliva spills from the mouth and as posterior if it pools in the pharynx, posing an aspiration risk. Drooling is considered normal in children up to 2 years; however, physiologic episodes occur later, particularly with teething (Reference 55).

In a study of children with CP attending special schools, 58% were found to drool, with 33% described as having severe drooling (Reference 56). Drooling can negatively affect social interactions, interfere with speech development and communication, and cause skin breakdown around the mouth and chin. In addition, drooling increases the difficulty of oral hygiene for patients and caregivers. In an assessment of participation issues in adolescents with CP, parents identified oral hygiene as their second-highest ranked problem when the adolescent was unable to communicate (Reference 57).

When a patient or parent presents with concerns about drooling, assessment should include a thorough history, a speech pathology examination of the oral region, a dental examination if the patient is older than 3 years, and a questionnaire to determine severity (Reference 54). The patient history should determine whether there is evidence of chronic aspiration, gastroesophageal reflux, feeding difficulties, or medications such as cholinergic drugs that could be contributing to the drooling. If present, these problems should be addressed (Reference 55).

In general, nonpharmacologic management is the first step to treatment of drooling. Patient and caregiver education on oral hygiene, attention to posture and positioning, and oral motor skills training may all provide benefit (Reference 55). After implementing these measures and addressing any dental issues, pharmacotherapy may be justified. Drug treatments include anticholinergic agents and botulinum toxin A products. Surgical management is another treatment possibility that is usually employed for more severe cases. Surgical procedures include redirection or excision of submandibular saliva ducts or parotid duct ligation (Reference 55).

Glycopyrrolate and scopolamine are the anticholinergic drugs most commonly used to treat sialorrhea. Their mechanism of action for drooling is to decrease the volume of saliva produced by blocking the cholinergic muscarinic receptors in the salivary glands. Unfortunately, they lack selectivity and are associated with other undesirable anticholinergic effects such as flushing, urinary retention, and constipation. Glycopyrrolate has the most available evidence on efficacy and a relative favorable adverse effect profile (Reference 58). A study reported a placebo-controlled, double-blind, dose-ranging, crossover study of glycopyrrolate in 39 pediatric outpatients with neurodevelopmental conditions and troublesome drooling (Reference 59). Most of the patients had CP and ranged in age from 4 to 19 years. They used a 4-week dose titration schedule, followed by 4 weeks of maintenance therapy with a 2-week washout and observation period before crossover. Twenty-seven children completed the study, and in those patients, drooling was significantly reduced on the basis of a 9-point scale. Adverse effects were common, occurring in 69% of the children during the glycopyrrolate arm; seven patients were receiving glycopyrrolate when they withdrew from the study because of an adverse effect. The most frequent adverse effects were behavioral changes, constipation, excessive oral dryness, and urinary retention. The authors recommended initiating therapy at 0.04 mg/kg/dose and increasing weekly up to 0.1 mg/kg/dose given two times/day in the morning and midafternoon (Reference 59). Glycopyrrolate was previously available only in a tablet formulation for oral administration. In July 2010, the FDA approved Cuvposa, an oral liquid formulation of glycopyrrolate, for chronic severe drooling in children aged 3–16 years with neurologic disorders (Reference 60). Dosing recommendations for the oral liquid formulation are to initiate therapy at 0.02 mg/kg/dose three times/day with increases of 0.02 mg/kg/dose at 5- to 7-day intervals if needed. The maximal recommended dose is 0.1 mg/kg/dose not to exceed 1.5–3 mg. Contraindications are medical conditions that preclude anticholinergic therapy and patients taking solid oral dosage forms of potassium chloride as glycopyrrolate may extend the time the potassium chloride is in the gastrointestinal tract increasing the risk of gastrointestinal irritation. Cuvposa is available as a 1 mg/5 mL concentration, and although expensive, a specialty pharmacy distribution system is available to help patients with insurance authorizations (Reference 60).

Scopolamine is administered transdermally to treat sialorrhea. Transderm Scop is commercially available as a 1.5-mg patch that delivers 1 mg of scopolamine over 3 days (Reference 61). It is licensed for adults to prevent motion sickness and for nausea and vomiting associated with recovery from anesthesia and surgery. The patch is placed on a hairless area behind the ear with alternating ear sites within the 3-day interval. The patch should not be cut, and hands should be washed thoroughly after placing and discarding (Reference 61). A study evaluated scopolamine for drooling in a placebo-controlled, double-blind, crossover trial (Reference 62). The study's investigators enrolled 30 patients with neurodevelopmental disorders and persistent drooling. Each patient received 2 weeks of transdermal scopolamine and placebo with a 1-week washout interval before crossover. Scopolamine was administered as a 1.5-mg patch changed every 72 hours. They found a significant reduction in baseline drooling on a 3-point scale with scopolamine but not placebo. Four patients discontinued the study because of adverse effects: one case of irritability, one case of agitation, and two patients had skin reactions (Reference 62). Another study found similar results in a smaller trial of 10 patients 5–18 years of age with neurodevelopmental disorders and moderate to severe drooling (Reference 63). This trial was placebo-controlled but not blinded and used the 1.5-mg transdermal scopolamine patch applied twice a week for 2 weeks with crossover to placebo. Scopolamine significantly reduced scores on a 6-point drooling scale compared with placebo. Pupil dilation was noted in two-thirds of the patients receiving scopolamine (Reference 63). Although transdermal scopolamine may be a reasonable treatment option for drooling in older children and adolescents, questions remain whether it is acceptable to use the dosing form in younger patients and as long-term therapy.

The Cerebral Palsy Institute developed an international consensus statement on the use of botulinum toxin for adult and pediatric drooling (Reference 54). For this unlabeled indication, it is given by intraglandular injection into the submandibular and parotid salivary glands. It works by inhibiting the release of acetylcholine from cholinergic nerve endings in the gland, causing a reduction in the secretion of saliva. On the basis of a review of clinical trials, the consensus statement recommends the use of botulinum toxin A in patients with a significant problem with drooling. It recommends excluding patients (1) if they have been given botulinum toxin A for any reason in the previous 3 months; (2) if they have antibodies against botulinum toxin A; or (3) if they are unfit for sedation or anesthesia (Reference 54).

The largest study to date reported on the use of onabotulinumtoxinA for drooling in 131 children and young adults with a mean age of 10.9 years (range 3–27 years), as a prospective cohort study (Reference

64). Children were included in the study if they had CP or another nonprogressive neurologic disorder and moderate to severe drooling. They received onabotulinumtoxinA injected into submandibular glands at a dosage of 15 units per gland for body weight less than 15 kg; 20 units per gland for body weight 15–25 kg; and 25 units per gland for body weight greater than 25 kg. A clinically notable response was reported in 46.6% of children, as defined by a significant reduction in direct observational drooling quotients and caretaker visual analog scales. Children who initially responded to onabotulinumtoxinA relapsed after a mean of 22 weeks (Reference 64). The length of response is consistent with the consensus paper statement that there should probably be a 4- to 6-month interval between injections (Reference 54). Various doses of botulinum toxin A have been used in studies, and as with the use of botulinum toxin A for spasticity, it is critical to identify a particular product used and not to interchange doses between products.

The consensus paper provided recommendations to prevent or minimize adverse events associated with botulinum toxin for drooling (Reference 54). Ultrasound guidance should be used for injection because it helps ensure intraglandular delivery as opposed to injection into surrounding tissue. Adverse effects related to trauma at the injection site include pain, hematoma, intraoral blood, swelling of the gland, and infection. Temporary swallowing difficulties may occur because of the swelling of the gland, and patients should be observed for at least 2 hours postinjection. If a swallowing problem persists, it may be caused by the diffusion of botulinum toxin into surrounding muscle tissue. Follow-up with the patient and his or her caregivers in the first week is recommended to assess for eating and drinking difficulties. Moist food or a pureed diet should be given for the first week after injection. It is important to be alert to thickening of the saliva, which can lead to swallowing or respiratory difficulties (Reference 54). As noted in the spasticity section, it is critical to monitor and counsel patients regarding adverse effects caused by the systemic spread of botulinum toxin.

Low BMD

Children with CP are at risk of developing low BMD, particularly with moderate to severe functional classification of CP. In a study of 117 patients from this population aged 2–19 years, the authors found a 77% prevalence of osteopenia as defined by BMD *z* scores of less than –2.0 in femur measurements (Reference 13). Despite a mean age of 9.7 years, 15% of patients had a history of at least one fracture (Reference 13). Risk factors for patients with CP to have low BMD include the inability to ambulate independently, feeding difficulties, use of antiepileptic drugs, and previous fracture (Reference 65). Low exposure to sunlight and lack of weight-bearing exercise are additional contributing factors to low BMD that have not yet been assessed in CP (Reference 65).

Figure 3 provides a treatment algorithm to identify and treat low BMD in patients with CP. The first steps in treatment are to reduce modifiable risk factors and ensure optimal nutritional intake, particularly of calcium and vitamin D (Reference 12). Measurement of 25-hydroxy vitamin D blood levels is helpful to determine whether a patient requires supplemental or treatment doses of vitamin D. Bisphosphonates are a pharmacologic treatment option in patients with a low BMD and history of fractures (Reference 12). Pamidronate has been studied in children with CP and osteopenia. In one retrospective review, the authors reported on longer-term rate of fracture in children with CP who had received about a 1-year course of intravenous pamidronate (Reference 66). They studied 25 children with severe CP (defined as GMFCS level IV or V) and at least one fracture before pamidronate for an observation period of 1–10.5 years after therapy. The patients received intravenous pamidronate on a protocol of 1 mg/kg/dose (maximum 35 mg) in normal saline, administered over 4 hours. This dose was given on 3 consecutive days every 3–4 months. The mean age of patients at the time of treatment was 11 years 2 months (range, from 3 years 10 months to 19 years 7 months). They found a significant decrease in the fracture rate during the observation period compared with pretreatment (13% vs. 30.6%). For most patients, the treatment effect lasted 4 years or longer (Reference 66). Patients who receive pamidronate should be monitored for infusion reactions, hypocalcemia, and other electrolyte abnormalities (decreased phosphate, potassium, and magnesium) (Reference 26). Serum creatinine should also be monitored because renal insufficiency has developed in patients taking pamidronate. In addition to pamidronate, alendronate has been investigated as treatment for osteopenia in children with cerebral palsy. In a small study, 26 children aged 3–17 years who had quadriplegic cerebral palsy and osteopenia were given alendronate 1 mg/kg/week with calcium and vitamin D supplementation for over a year. With treatment, lumbar vertebral bone mineral density increased over pretreatment values. None of the children had to interrupt treatment due to an adverse effect and there were no cases of esophageal irritation reported (Reference 67). However, patients should be counseled to stand or sit for administration of alendronate followed by an upright

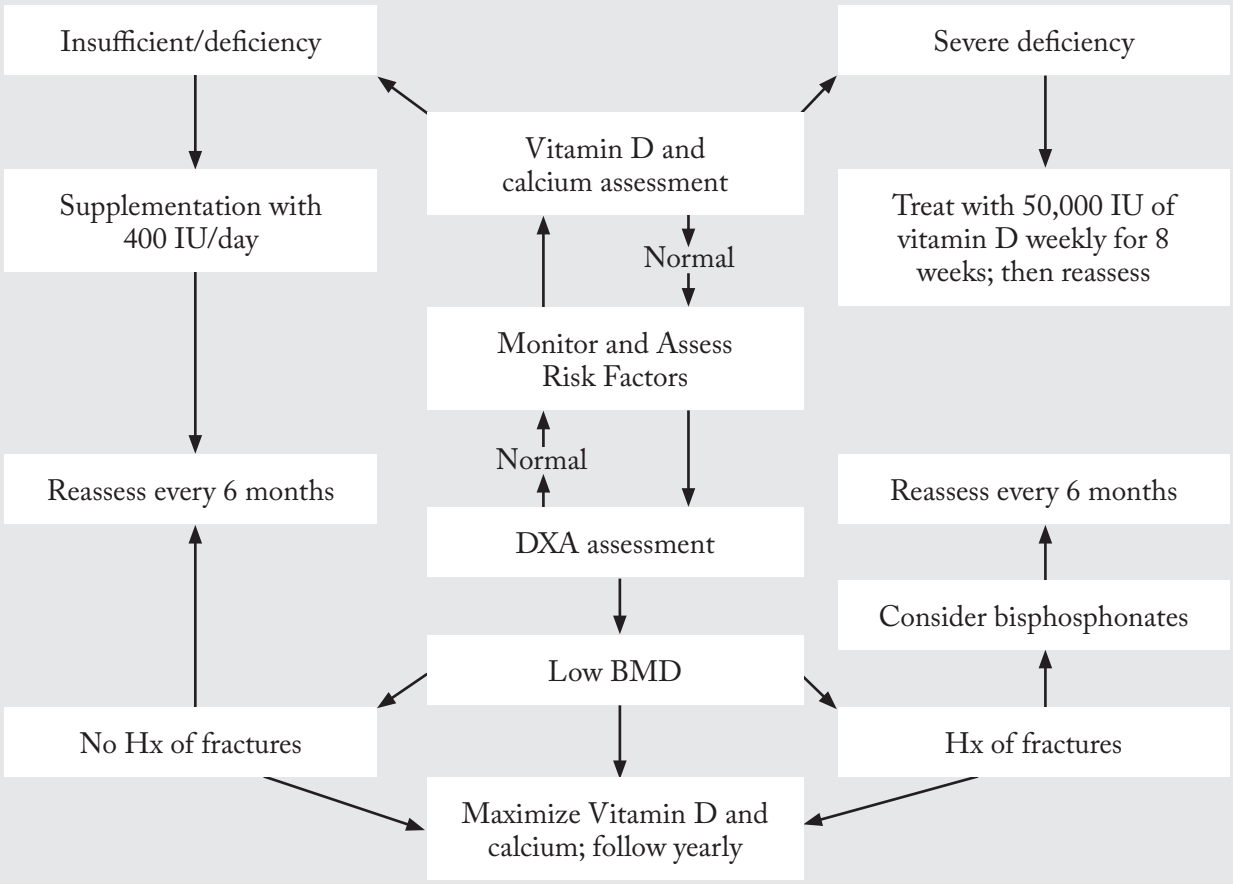


Figure 3. Assessment, prevention, and treatment of low bone mineral density in patients with cerebral palsy.

BMD = bone mineral density; DXA = Dual-energy X-ray absorptiometry; Hx = history; IU = international units.
Reproduced from Houlihan and Stevenson (Reference 12) with permission.

posture for 30 minutes. These recommendations may limit the use of alendronate in young children and in patients with more severe CP. Osteonecrosis of the jaw is a relatively infrequent, but worrisome adverse effect associated with biphosphonates. Although this adverse effect has occurred primarily in patients with cancer, patients with CP may have a theoretical increased risk if poor oral hygiene is present. A dental examination is warranted in a patient with CP before he or she undergoes treatment with a bisphosphonate.

Conclusions

Cerebral palsy is a multifaceted disorder in childhood because of motor disabilities and challenging co-impairments. Children with CP are recommended to receive quality care through a primary care medical home model with multidisciplinary and community input (Reference 68). Comprehensive treatment plans are used to optimize function, capabilities, quality of life, and aesthetics. Pharmacotherapy is an important component of treatment, and a pediatric pharmacist provides valuable support to the medical home, especially as the number and complexity of treatment options for spasticity and other conditions associated with CP increase.

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CHAPTER 26

Seizure Disorders

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Learning Objectives

1. Describe types of seizures common in children.
2. Identify pharmacologic treatment options for different seizure types in children.
3. Recognize common adverse effects from anticonvulsant therapy specific for children.
4. Describe treatment for status epilepticus in children.

Abbreviations in This Chapter

EEG	Electroencephalographic
GABA	γ-aminobutyric acid
NMDA	*N*-methyl-D-aspartate

Introduction

A seizure is a change in function or behavior caused by a paroxysmal electrical discharge of neurons in the brain (Reference 1). Seizure type varies depending on the area within the brain of the discharge, the direction and speed of the electrical impulse, and the age of the child. Epilepsy is defined as two or more seizures that occur without acute provoking factors (References 1, 2). Not all seizures lead to a diagnosis of epilepsy. There is a wide array of causes and classifications of epilepsies in children. An epileptic syndrome is a group of signs and symptoms that occur with a specific neurologic and electroencephalographic (EEG) finding. Idiopathic epilepsies refer to presumed genetic syndromes without structural brain abnormalities, whereas symptomatic epilepsies result from a structural brain lesion, which is identified (Reference 3). A seizure that lasts more than 30 minutes or two or more seizures that occur without a return to consciousness in between are termed *status epilepticus* (Reference 1). Seizures may be short without repercussions; however, prolonged seizures may be life threatening.

The treatment of seizures and epilepsies varies per condition. Some seizure types do not require any interventions, whereas others may require one or more anticonvulsant drugs to prevent a seizure from occurring. Potential nonpharmacologic therapies such as the ketogenic diet may be tried in certain patients with the goal of obtaining seizure control. Each patient is individually treated for his or her specific seizure disorder. The anticonvulsant medications in general have shown efficacy for seizures; however, adverse reactions and dosing formulations of specific medications may limit their use in subgroups of the pediatric population. Thus, pharmacologic therapy for children should be monitored frequently and carefully. Controversy exists regarding switching patients from brand to generic drug formulations as more generic drugs become available and provide a decrease in cost for care. Many factors, such as those described, affect the selection of a pharmacologic treatment plan for each patient.

Epidemiology

Seizures are the most common neurologic disorder of childhood (Reference 1). They occur in about 4% to 10% of children and account for 1% of all emergency department visits (References 4, 5). Annually, 150,000 children experience an unprovoked first seizure, with 30,000 of these children developing epilepsy (Reference 4). Children younger than 3 years have the highest incidence of seizures, with the incidence decreasing as the child ages (Reference 6). For children with epilepsy, 10% to 25% will develop status epilepticus (Reference 7). The highest risk is in those younger than 1 year.

Etiology

Pathophysiology

A seizure is a result of the hypersynchrony of neuronal discharges of which the etiology varies (Reference 1). Mechanisms that promote seizure activity include the following: (1) ion channel problems (sodium and calcium, voltage regulated, inactivation gate), (2) decreased inhibition (γ-aminobutyric acid [GABA], adenosine), (3) excitatory neurotransmission (glutamate, *N*-methyl-D-aspartate [NMDA]), and (4) alteration in the extracellular concentration of potassium and calcium. Thus, pharmacotherapy is directed to one or more of these mechanisms.

Oxygen and glucose consumption, as well as lactate and carbon dioxide production, is increased during a seizure. Adequate ventilation usually compensates for these changes, but prolonged seizures or inadequate ventilation may lead to hypoxia, hypercarbia, and

respiratory acidosis, possibly resulting in permanent damage (Reference 1). Hypoglycemia, hyperthermia, hyperkalemia, lactic acidosis, or rhabdomyolysis can also occur from a prolonged seizure.

Several medical conditions can precipitate seizures. Children with developmental delay or cerebral palsy are at a higher risk of developing seizures. From 3% to 10% of children with head trauma will experience a seizure, usually in the first 24 hours post-accident (Reference 8). Most children have a good prognosis post-trauma without neurologic repercussions. Other secondary causes of seizures include cerebrovascular disease, neurodegenerative or developmental disorders, tumors, metabolic disorders, drug ingestion or withdrawal, and central nervous system (CNS) infections (Reference 1).

Neonatal seizures are usually a consequence of perinatal or intrauterine hypoxia (50% to 65%) (Reference 1). Intracranial hemorrhages are responsible for 15%, whereas 5% to 10% of cases are related to metabolic abnormalities, infections, and toxins. Pyridoxine, glucose, and calcium deficiencies are common metabolic etiologies.

Genetic Basis

At least 20% of epilepsies have been linked to a genetic component (Reference 9). Epilepsies termed *idiopathic* are presumed to be genetic in origin (Reference 7). Benign rolandic epilepsy and benign familial neonatal seizure have an autosomal dominant inheritance. Absence and tonic-clonic seizures show a genetic component (Reference 10). Febrile seizures also show a genetic component, with 25% to 40% of patients having a family history (Reference 1). The $GABA_A$ and acetylcholine receptors, as well as sodium, potassium, and chloride channels, have all been implicated in genetic abnormalities (Reference 10). Molecular genetic studies of different seizure types and syndromes are ongoing.

Clinical Presentation and Diagnosis

Signs and Symptoms

During a seizure, extremities may physically convulse, go limp, or stiffen. One extremity or all may be involved in the seizure. Usually, a health care provider will not witness the seizure, therefore having to rely on someone else's description of the event. Specific signs and symptoms of a seizure depend on the type of seizure. An aura may precede a seizure. In children, the most common types of aura are a feeling of fear or epigastric pain and discomfort; however, children may have difficulty describing this (Reference 9). After a seizure, a period of fatigue, confusion, or irritability occurs (Reference 1). This is defined as the postictal period. The presence of cyanosis, vocalizations, loss of sphincter tone, and posture of the patient should be noted when describing the seizure (Reference 9).

Box 1. Seizure type and characteristics (References 7, 9, 11, 12).

- ***Partial*** (begins locally, involves one cerebral hemisphere, unilateral motor manifestations)
  - Simple: No loss or impairment of consciousness
  - Complex: Loss or impairment of consciousness/altered mental status occurs
  - Secondary generalization: Presents initially as partial, but spreads to generalized tonic-clonic seizure
- ***Generalized*** (involves bilateral cerebral hemispheres without local onset, bilateral motor manifestations)
  - Absence: Sudden cessation of motor activity, brief loss of awareness, and blank stare
    - Simple: Not associated with postictal period
    - Complex: Associated myoclonic activity and altered consciousness
  - Myoclonic: Shocklike muscular contractions of the face, trunk, and extremities
  - Clonic: Rhythmic jerking and flexor spasms of the extremities
  - Tonic: Sustained contraction of muscles with progressive rigidity
  - Tonic-clonic: First tonic symptoms; then clonic
  - Atonic: Sudden loss of muscle tone and consciousness
  - Infantile spasms: Spasmodic clusters of jerking contractions of the extremities, head, and trunk
- ***Unclassified*** – All seizures unable to be classified because of incomplete or inadequate data
- ***Status Epilepticus*** – Seizure lasting more than 30 minutes or two or more seizures occurring in which the patient does not regain consciousness between episodes

The International League Against Epilepsy has classified seizures as four major types, as follows: partial, generalized, unclassified, and status epilepticus (Reference 11). Definitions and characteristics of these seizure types are provided in Box 1. The most common childhood seizure type is generalized tonic-clonic (Reference 12). Simple and complex partial seizures will progress to generalized tonic-clonic seizures in 30% of children. Status epilepticus will be the presenting seizure in 10% to 12% of children experiencing their first unprovoked seizure (Reference 13). Several pediatric epilepsy syndromes also exist. The International League Against Epilepsy has created a classification of epilepsies and epileptic syndromes (Reference 14). Some of the more commonly seen syndromes will be presented in this chapter.

Neonatal seizures occur in 1.8–3.5 of every 1000 newborns because of the immaturity of the neonatal brain (Reference 1). Signs and symptoms are usually atypical and include eye deviations, lip smacking, or apneic episodes. Seizures in this population generally cause little brain injury, but low-birth-weight infants tend to have a higher incidence and worse outcomes of seizures. A benign familial neonatal seizure is a syndrome that usually presents within the first 3 days of life and resolves spontaneously by age 6 months. "Fifth-day fits" are known as benign idiopathic neonatal convulsions that appear at day 5 of life and end by day 15 of life.

Infantile spasms usually occur during the first year of life (Reference 10). They are quick symmetrical contractions of the neck, trunk, and extremities that occur in clusters for less than 5 seconds (Reference 15). Abduction or adduction of the upper extremities can be seen with flexion or extension of the neck, and these clusters may be repeated several times a day (Reference 10). West syndrome is a disorder with three specific characteristics, as follows: infantile spasms (flexor, extensor, or mixed spasms); a particular EEG pattern (hypsarrhythmia); and developmental arrest or delay (Reference 15). In around 70% of children, developmental delay is seen before the onset of spasms (Reference 10). Diagnosis usually occurs between age 4 and 18 months, with a peak age of 4–7 months (Reference 12). Males are affected more than females, and most patients (95%) have developmental delay. Tuberous sclerosis is seen in 25% of children with infantile spasms (Reference 1).

Lennox-Gastaut syndrome accounts for 2.9% of all epilepsies (Reference 10). This syndrome is characterized by a mixture of intractable seizures such as tonic, myoclonic, atonic, and absence (References 1, 12). Tonic seizures generally occur during sleep, and absence seizures are usually atypical in characteristic (Reference 10). Children also tend to have developmental delay and severe behavioral issues. The onset is usually between age 3 and 10 years, with a peak incidence at 3–5 years (Reference 10). Around 40% of patients have previously been given a diagnosis of infantile spasms. Seizure control is extremely difficult in patients with Lennox-Gastaut syndrome. Most of these patients will take several anticonvulsant medications, yet they will still experience seizures.

Another syndrome is benign rolandic epilepsy (benign childhood epilepsy with centrotemporal spikes), which manifests typically as seizures while sleeping. Clonic movements in the face usually wake the child from sleep. Twenty percent of patients have only one seizure, whereas 25% have repeated clusters (Reference 9). It typically occurs in children aged 3–13 years and is generally benign, as the name states. Most patients outgrow the seizures by young adulthood. The peak age of onset is age 9–10 years (Reference 9).

Juvenile myoclonic epilepsy (Janz syndrome) usually occurs in 12- to 18-year-old adolescents and presents as myoclonic jerks on waking (Reference 12). Most patients (80%) also have tonic-clonic seizures, and some have absence seizures (25%) as well. Hormonal changes, stress, alcohol, and sleep deprivation can provoke these seizures.

Febrile seizures are classified as a "special syndrome" (References 3, 15). Febrile seizures are defined as a seizure that is accompanied by a temperature of 100.4°F (38°C) or greater in children between age 6 months and 5 years (Reference 16). The child must not have a diagnosis of a CNS infection, and the temperature may be obtained by any method. Febrile seizures are not related specifically to the peak degree of temperature, but rather, to the rate of temperature rise. The specific mechanism for a febrile seizure is unknown, but it is hypothesized that fever lowers the seizure threshold (Reference 1). Febrile seizures are the most common type of convulsive event that occurs in children younger than 5 years, occurring in 2% to 5% of all children (Reference 15). The peak onset is age 14–18 months (Reference 9). Febrile seizures are characterized as simple or complex. Simple febrile seizures are primary generalized seizures that last less than 15 minutes and do not recur within 24 hours (Reference 16). Complex febrile seizures are focal, last 15 minutes or longer, and/or recur within 24 hours. Most febrile seizures are benign and self-limited, and 80% are classified as simple. No long-term effects from simple febrile seizures have been identified (References 12, 16). Children without risk factors are not at a higher risk of developing epilepsy by age 7 years than the general population (Reference 16). Those with risk factors such as multiple simple febrile seizures, first onset of febrile seizures that occurred at younger than 12 months, and family history of epilepsy are at a 2.4% risk of receiving a diagnosis of generalized afebrile epilepsy by age 25 years.

Diagnostic Criteria

Laboratory Data

No specific laboratory data diagnostic test for epilepsy exists, except when evaluating for metabolic or infectious causes of seizures (glucose, electrolytes, cerebral spinal fluid cultures, etc.). Prolactin may be transiently elevated after an acute episode for some seizure types, such as generalized tonic-clonic or complex partial seizures (Reference 17). Prolactin is thought to be released from the pituitary, which is controlled by the hypothalamus. It is theorized that a seizure can alter the hypothalamus relation. It is best to obtain the level 10–20 minutes postseizure. An elevated prolactin may help differentiate psychogenic nonepileptic seizures from epileptic seizures in adolescents. Serum prolactin use has not been determined for other circumstances (status epilepticus, repetitive seizures, neonatal seizures).

Procedures

An EEG is helpful in the diagnosis of various epileptic seizure types or syndromes because most have a characteristic EEG wave. An EEG should be performed after the second seizure but may be performed after the first seizure in certain circumstances (Reference 3). It should not be used solely to confirm or exclude a diagnosis of seizures. Clinical history should always be considered when evaluating a diagnosis. Repeated EEGs are typically not indicated once a diagnosis is confirmed. However, a sleep-deprived, video, or continuous EEG may be tried if an interictal EEG is normal or for complicated cases (Reference 9). A continuous EEG with video recording (24–72 hours) is optimal but challenging to obtain because it usually involves admitting a patient to a hospital setting. An EEG is best obtained during a seizure; however, abnormal wave patterns may be present during the postictal state. Many times, the EEG between seizure episodes will be normal, limiting the test's utility. An EEG is not recommended in a patient with simple febrile seizures who is neurologically healthy (Reference 18).

Specific EEG wave patterns are characteristics for certain epileptic syndromes. Lennox-Gastaut syndrome shows as a slow, irregular, high-voltage spike pattern (Reference 6). Benign rolandic epilepsy has as perisylvian spiking pattern (Reference 12). Juvenile myoclonic epilepsy shows a pattern of fast spike and wave discharges. Hypsarrhythmia, seen in infantile spasms, shows random high-voltage slow waves with multifocal spikes. Absence seizures present as regular and symmetrical spike-and-slow-wave complexes (Reference 11). Clonic seizures show fast activity with slow waves, whereas tonic seizures show fast activity that decreases in frequency but increases in amplitude. Atonic seizures show as polyspikes and slow waves.

Neuroimaging is useful in identifying structural abnormalities (Reference 3). A magnetic resonance imaging (MRI) is the test of choice for epilepsy. A computed tomography scan should be used when urgent assessment is necessary or an MRI is contraindicated.

Course and Prognosis of Disease

Most children who experience a first-time unprovoked seizure will likely not have another seizure (Reference 13). Risk factors for recurrence of seizures include an abnormal EEG, symptomatic cause, seizure while sleeping, history of febrile seizures, or postictal paresis (Reference 10). Of patients with a diagnosis of new-onset epilepsy, two-thirds will become seizure free with the first or second medication administered (Reference 19). In children with an unprovoked first seizure, the recurrence rate is 3% to 50% by 2 years (Reference 13). In a child presenting with status epilepticus as the first seizure, the recurrence rate is similar to those presenting with a brief first seizure. However, if they experienced a subsequent seizure, there is an increased risk of its being prolonged. One-third of children with simple febrile seizures will have a recurrence (Reference 16). The highest risk of recurrence is in children who experience their first febrile seizure before age 1 year (Reference 1). The second febrile seizure tends to occur within 6 months of the first one.

The prognosis of epilepsy is difficult to predict for each patient. Recurrence and relapse rates differ by type of seizure or syndrome. West and Lennox-Gastaut syndromes do not have a favorable prognosis. Benign rolandic epilepsy remits without relapse, whereas absence seizures have a 12% relapse rate, and juvenile myoclonic epilepsy has an 80% rate (Reference 10). Simple febrile seizures are usually outgrown by age 5 years.

Mortality from seizures or epilepsy also varies by type. In children, mortality rates of up to 16% have been associated with status epilepticus (Reference 7). As the duration of status epilepticus is prolonged, mortality rates increase (Reference 20). Neonates with status epilepticus tended to have the highest mortality and neurologic sequelae. Patients with infantile spasms have a 20% mortality rate (Reference 12). However, patients with simple febrile seizures are not at increased mortality risk (Reference 16).

Treatment

Therapy Goals

In an actively seizing patient, airway stabilization and termination of the seizure without recurrence are priorities. Once the seizure has stopped, diagnostic studies may be obtained to determine the etiology. Patients are placed on anticonvulsant medications to improve their

quality of life by decreasing the number of seizures they experience, with the ultimate goal of being seizure free. However, less than 50% of patients become seizure free; thus, most pharmacologic therapies are lifelong treatments, and chronic adverse effects must be considered (Reference 7).

The initiation of pharmacologic treatment is usually withheld until after the second seizure occurs because studies have not shown that treatment after the first seizure improves the long-term prognosis of remission (Reference 13). However, clinical decisions weighing the individual's risks and benefits of anticonvulsant therapy and the incidence of a subsequent seizure must be evaluated.

Nonpharmacologic Therapy

Few nonpharmacologic therapies exist for seizures. The ketogenic diet is a popular therapy with patients who have refractory seizures and whose many medications for treatment have failed. The ketogenic diet is recommended for consideration in those with symptomatic generalized epilepsy (Reference 21). This diet consists of low protein and carbohydrate intake with high-fat meals, thus inducing ketosis in the patient. A ketogenic state has been shown to reduce seizure frequencies by 50% to 70% in some studies, but a specific mechanism of action is unknown (Reference 1). Patients are sometimes hospitalized during the initiation of the diet to monitor for hypoglycemia, dehydration, and vomiting. Long-term adverse effects include weight loss, hyperlipidemia, hypoproteinemia, nephrolithiasis, renal tubular acidosis, constipation, growth retardation, and increases in hepatic and pancreatic enzymes (Reference 1). Some patients may develop a prolonged QT interval; thus, this must be evaluated for cardiomyopathy (References 12, 21). All patients should be monitored routinely and will need vitamin supplementation. Patients on the ketogenic diet should not be initiated on valproic acid because of the risk of hepatotoxicity. Dextrose should also not be administered intravenously or by medications to a patient on the ketogenic diet because it may result in increased seizures (Reference 12). Many liquid forms of medications contain sugars or carbohydrates. The *Pediatric & Neonatal Dosage Handbook* traditionally provides a table of the carbohydrate amount in medications, which will assist pharmacists in providing information to the parent (Reference 22). The ketogenic diet requires strict control and adherence. Today, similar diets such as the modified Adkins and low Glycemic Index Treatment may be more tolerable and do not require inpatient initiation (Reference 12).

Vagal nerve stimulation used as adjunctive therapy for those with refractory epilepsy has resulted in a decrease of seizures. It is reserved for children 12 years and older who have partial-onset seizures; however, off-label use extends to primary generalized epilepsy (Reference 7). The stimulator is placed under the skin with an electrode wrapped around the left vagus nerve. In studies, 23% to 50% of patients had a decrease in seizures by 50% or greater (Reference 7). Adverse effects such as hoarseness, cough, dyspepsia, nausea, and pain are generally tolerable. Serious adverse effects such as infections and nerve paralysis have been seen (Reference 7).

Surgical treatment is an option in patients with refractory focal epilepsy. The precise location of the epileptogenic area in the brain must be known. The average time from diagnosis to surgery ranges from 12 to 15 years (Reference 10). Temporal lobectomy is the most common surgery, with a 78% result of seizure freedom (Reference 18). A hemispherectomy or corpus callosotomy procedure may also be considered to control seizures in certain patients. Each surgery has risks; thus, each must be compared with possible benefits for the child.

Pharmacologic Therapy

Pharmacologic treatment for seizures depends on the etiology and type of seizure or syndrome. Seizures caused early by head trauma seldom require medications (Reference 10). However, phenytoin, carbamazepine, or levetiracetam may be used prophylactically until acute neurologic signs have resolved to prevent early seizures. Seizures with metabolic causes such as hypoglycemia or hypocalcemia are treated by correcting the underlying etiology. Seizures secondary to infections such as meningitis should cease after the infection is identified and treated.

Pharmacologic treatment is typically indicated in patients with epilepsy. Monotherapy is preferred for patients, but combination therapy may be required for seizure control. Several trials of monotherapy with different anticonvulsants may be evaluated for efficacy before using combinations. After therapy is initiated, patients can be categorized into two groups: treatment-responsive or treatment-resistant (Reference 19). After the first or second medication is administered, two-thirds of patients will become seizure free. Unfortunately, 20% to 30% of patients will have uncontrolled or intractable seizures despite therapy, or they will experience significant adverse effects from the anticonvulsant medications (Reference 23).

Several anticonvulsants are available today for treatment. The "older" anticonvulsants are as follows: carbamazepine, phenobarbital, phenytoin, primidone, valproic acid, and ethosuximide. They share many characteristics such as complex pharmacokinetics, which require monitoring, and many drug interactions caused by hepatic induction or inhibition. The second-generation anticonvulsants are as follows: felbamate, gabapentin,

lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide. These eight medications came on the market between 1993 and 2000 and have a more favorable drug profile because of fewer drug interactions and kinetics that do not require monitoring. The newest anticonvulsants to be approved are pregabalin (2004), rufinamide (2008), lacosamide (2008), vigabatrin (2009), ezogabine (2011), and clobazam (2011). Specific mechanisms of action have not been found for most anticonvulsants, but hypothesized or in vitro actions are usually provided in reference books. Most of the anticonvulsants are initially approved for use in adolescents and/or adults. After time, pediatric studies or reports from the literature will emerge, with potential pediatric indications following. As of today, not all the anticonvulsants listed are U.S. Food and Drug Administration (FDA) approved for use in children, but for most medications, pediatric dosing can be located. Table 1 lists recommended medications and corresponding seizure types. Table 2 provides the pediatric dosing of anticonvulsants, but it does not include all seizure types and ages.

Many factors must be considered before selecting an anticonvulsant for a patient. First, the medication choice will be based on the efficacy data available for the diagnosed seizure type. Not all anticonvulsants treat all seizure types. Next, characteristics of the patient such as age, comorbid disease states, concomitant medications, ability to take medications, lifestyle, and preference of the child/caregivers are considered. Medication characteristics are also evaluated such as drug interactions, adverse effects, cost, and dosage forms. Many anticonvulsants are unavailable in pediatric-friendly dosage forms, thus limiting their use. Adverse effects are an issue with all the anticonvulsants. Some of these effects are more prominent or occur only in the pediatric population. In general, medication selection should focus on an effective, tolerable drug with the least risk of harm for the patient. Many anticonvulsants are teratogenic; thus, patients of childbearing age must be educated on the possible fetal effects, or select medications may be avoided. Serum pregnancy tests may be obtained in these patients before initiating medication. All anticonvulsants must be initiated at low dosages and titrated slowly to a therapeutic dose. Fast titration or starting at higher dosages than recommended may cause increased adverse effects in the patient. Table 2 lists anticonvulsant medications with characteristics focused on pediatrics.

Controversy exists over the use of generic anticonvulsants in patients. Bioequivalence studies are conducted comparing a single dose of the generic with the brand formulation, not generic versus generic formulations (Reference 27). In addition, generic drugs are not required to complete bioequivalence studies in children unless the drug is targeted to this population. Most anticonvulsants have several generic formulations available. However, the "older" anticonvulsants have more variable pharmacokinetics and are narrow therapeutic index drugs, unlike most of the "newer" anticonvulsants. Variability in pharmacokinetic parameters, especially between generic formulations, may cause an alteration of clinical efficacy in the patient. Breakthrough seizures in stable patients could result in harm to themselves or others, emotional distress, or loss of driving privileges or employment. Three case-controlled analyses using large national patient medical claims databases found that those who had a recent switch in formulation (brand-to-generic, generic-to-generic, or generic-to-brand) experienced an increase in epilepsy-related events requiring acute care (References 28–30). Cost and supply chain inconsistency also affects the decision to substitute medications. Because of concerns and lack of controlled, prospective data, patients should be initiated and remain on the same formulation consistently. Children who are stable on their current regimen should not have their regimen altered.

Status Epilepticus

Status epilepticus is treated on the basis of etiology. A patient history can be very helpful as well. If hypoglycemia is present, intravenous infusions of dextrose are required. Some sources recommend glucose administration in all patients in status. Sodium and calcium levels should also be evaluated, and treatment should be initiated if abnormal values are confirmed. If a CNS infection is hypothesized, antibiotics are warranted. Status epilepticus is aggressively treated with medication if the seizure lasts more than 5 minutes. Benzodiazepines (lorazepam, diazepam, midazolam) can be administered once or twice; they will generally stop the seizure in 2–3 minutes (Reference 31). All benzodiazepines are equally effective for seizure cessation (References 20, 31). However, a Cochrane Database Review found lorazepam to be safer than diazepam in children (Reference 32). Diazepam has a longer half-life, but lorazepam has a smaller volume of distribution; thus, it stays in the CNS longer. Diazepam and lorazepam may be administered intravenously. If prehospital care is required and intravenous access is unavailable, both diazepam and lorazepam can be administered rectally, and midazolam may be administered intramuscularly, buccally, or intranasally. In fact, one study even found buccal midazolam more effective than rectal diazepam (Reference 32).

If benzodiazepines are not effective in terminating the seizure or if seizures recur after successful treatment with a benzodiazepine, phenytoin, fosphenytoin, or phenobarbital can be used as secondary agents. Phenytoin must be administered in a large vein to decrease the risk of extravasation. In addition, because of its vehicle (40%

Table 1. Medication Options by Type of Seizure (References 3, 10, 23–25)

Type of Seizure	Drugs of Choice	Alternatives	Drugs That May Worsen Seizure Type	FDA Approved (age of approval varies per medication)
Partial	*(newly diagnosed)* Carbamazepine Gabapentin Lamotrigine Oxcarbazepine[a] Phenobarbital Phenytoin Topiramate Valproic acid *(refractory monotherapy)* Lamotrigine Oxcarbazepine Topiramate *(refractory adjunctive)* Gabapentin[a] Lamotrigine[a] Levetiracetam Oxcarbazepine[a] Tiagabine Topiramate[a] Zonisamide	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Phenobarbital[a] Phenytoin[a] Topiramate[a] Valproic acid[a]		Carbamazepine Ezogabine Felbamate Gabapentin Lacosamide Lamotrigine Levetiracetam Oxcarbazepine Phenobarbital Phenytoin Pregabalin Tiagabine Topiramate Valproic acid Zonisamide
Absence	Lamotrigine	Ethosuximide Valproic acid	Carbamazepine Gabapentin Oxcarbazepine Phenobarbital Phenytoin Tiagabine Vigabatrin	Ethosuximide Valproic acid
Generalized tonic-clonic	Lamotrigine Topiramate Oxcarbazepine	Carbamazepine[a] Lamotrigine Oxcarbazepine Phenobarbital[a] Phenytoin[a] Topiramate[a] Valproic acid[a]	Tiagabine Vigabatrin	Carbamazepine Lamotrigine Levetiracetam Phenobarbital Phenytoin Topiramate

[a]Specific recommendation for children.

propylene glycol), administration-related hypotension and cardiac arrhythmias may occur. Fosphenytoin is a water-soluble prodrug of phenytoin with a lower pH. Fosphenytoin is preferred to phenytoin because of its faster administration rate and ability to be administered intramuscularly. Although fosphenytoin may be an improved agent on the basis of its characteristics, cost may limit its use in some health care settings. Phenobarbital is another option for use to abate status and has been found to be as efficacious as phenytoin (Reference 31). Several loading doses of phenobarbital may be administered, followed by maintenance dosing after the seizure has been stopped. Phenobarbital should not be administered intramuscularly for status epileptics because of its slow absorption. Decreased respirations and consciousness are adverse effects of phenobarbital.

Status epilepticus that fails to cease after two adequate doses of benzodiazepines, phenytoin/fosphenytoin, or barbiturates is deemed refractory. Refractory status epilepticus is more difficult to treat the longer it

Table 2. Characteristics of Anticonvulsants (References 3, 10, 22, 24–26)

Anticonvulsant Generic (trade name)	Molecular Target	Pediatric Dosing/Therapeutic Levels	Dosage Formulations	Adverse Effects (Pediatrics Focused)	CYP Drug Interactions
Carbamazepine (Tegretol, Tegretol-XR, Carbatrol, Epitol)	Sodium channel	< 6 yr: Initial: 10–20 mg/kg/day div BID or TID (suspension: QID); max: 35 mg/kg/day 6–12 yr: Initial: 100 mg BID (suspension: 50 mg QID); increase by 100 mg/day weekly; maintenance: 400–800 mg/day; max: 1000 mg/day > 12 yr: Initial: 200 mg BID (suspension: 100 mg QID), increase by 200 mg/day weekly; maintenance: 800–1200 mg/day; max: 12–15 yr: 1000 mg/day, > 15 yr; 1200 mg/day Adjust dose in renal impairment; use with caution in hepatic impairment. Therapeutic levels: 4–12 mcg/mL	ER capsule, suspension, tablet, chewable tablet, ER tablet, ext suspension	Boxed warnings: Aplastic anemia, agranulocytosis, dermatologic reactions (SJS, TEN), use in Asian patients with genotype: *HLA-B*1502* allele Accommodation disorders (blurred vision, diplopia, ataxia, and nausea), SIADH	Major 3A4 and minor 2C8 substrate; strong 1A2, 2B6, 2C8, 2C9, 2C19, 3A4 inducer, P-glycoprotein
Clobazam (Onfi)	$GABA_A$ receptor	< 2 yr: 0.5–1 mg/kg/day > 2 yr: ≤ 30 kg: Initial: 5 mg, increase to 10 mg at day 7, and increase to 20 mg at day 14; > 30 kg: Initial; 10 mg, increase to 20 mg at day 7, and increase to 40 mg at day 14 Doses > 30 mg should be divided. Adjust dose in renal impairment; contraindicated in severe hepatic impairment	Tablet	Somnolence, sedation, drooling, constipation, cough, urinary tract infection, aggression, insomnia, dysarthria, fatigue, suicidal behavior and ideation	Major 2C19 and 3A4 substrate
Ethosuximide (Zarontin)	Sodium and calcium channels	< 6 yr: Initial: 15 mg/kg/day div BID, increase every 4–7 days; maintenance: 15–40 mg/kg/day; max: 1.5 g/day ≥ 6 yr: 250 mg BID, increase by 250 mg/day every 4–7 days; maintenance: 20–40 mg/kg/day; max: 1.5 g/day Use with caution in renal and hepatic impairment. Therapeutic levels: 40–100 mcg/mL; toxic: > 150 mcg/mL	Capsule, solution, syrup	Nausea, headache, drowsiness	Major 3A4 substrate
Ezogabine (Potiga)	Potassium channel	≥ 18 yr: Initial: 100 mg TID, increase weekly by 150 mg/day; maintenance: 200–400 mg TID; max: 1200 mg/day Adjust dose in renal and hepatic impairment.	Tablet	Urinary retention, dizziness, somnolence, QT prolongation, neuropsychiatric symptoms (adult data)	Not cytochrome-dependent
Felbamate (Felbatol)	Sodium channel, $GABA_A$ and NMDA receptors	2–14 yr w/LGS: 15 mg/kg/day div TID or QID, increase by 15 mg/kg/day weekly; max: 45 mg/kg/day or 3600 mg/day ≥ 14 yr: Adjunct and conversion to monotherapy: 1200 mg/day div TID or QID, increase by 1200 mg/day weekly; max: 3600 mg/day; monotherapy: increase by 600 mg/day every 2 weeks Adjust dose in renal impairment.	Suspension, tablet	Boxed warnings: Aplastic anemia, acute hepatic failure Anorexia, somnolence, insomnia, vomiting, weight loss (usually first 3 months of treatment), nausea, gait abnormality	Minor 2E1 and major 3A4 substrate; weak 2C19 inhibitor; weak 3A4 inducer
Gabapentin (Neurontin)	Calcium channel	3–12 yr: Initial: 10–15 mg/kg/day div TID, maintenance: 3–4 yr: 40 mg/kg/day, 5–12 yr: 25–35 mg/kg/day > 12 yr: Initial: 300 mg TID; maintenance: 900–1800 mg/day; max: 3600 mg/day Adjust dose in renal impairment	Capsule, solution, tablet	Somnolence, fatigue, emotional lability, behavior changes, hostility, hyperkinesia, dizziness, fever	Not cytochrome-dependent

(continued)

Table 2. Characteristics of Anticonvulsants (References 3, 10, 22, 24–26) *(continued)*

Anticonvulsant Generic (trade name)	Molecular Target	Pediatric Dosing/Therapeutic Levels	Dosage Formulations	Adverse Effects (Pediatrics Focused)	CYP Drug Interactions
Lacosamide (Vimpat)	Sodium channel	≥ 17 yr: Initial: 50 mg BID, increase by 100 mg/day weekly; maintenance: 200–400 mg/day Adjust dose in hepatic and renal impairment.	Injection, solution, tablet	Prolonged PR interval, dizziness, headache, diplopia (adult data)	Carbamazepine, phenobarbital, and phenytoin may decrease lacosamide levels.
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR)	Sodium and calcium channels, inhibits glutamate release	2–12 yr: Immediate release: Initial: 0.3 mg/kg/day div one or two doses for weeks 1 and 2; increase to 0.6 mg/kg/day div BID for weeks 3 and 4; increase as needed by 0.6 mg/kg/day every 1–2 weeks; maintenance: 4.5–7.5 mg/kg/day div BID; max: 300 mg/day div BID With valproic acid–containing regimens: 0.15 mg/kg/day div one or two doses for weeks 1 and 2; increase to 0.3 mg/kg/day div BID for weeks 3 and 4; increase as needed by 0.3 mg/kg/day every 1–2 weeks; maintenance: 1–5 mg/kg/day div BID; max: 200 mg/day div one or two doses; *for patients > 6.7 kg and < 14 kg, initial dosing is 2 mg QOD in weeks 1 and 2; then 2 mg/day for weeks 3 and 4 With enzyme-inducing regimens, without valproic acid: Initial: 0.6 mg/kg/day div BID for weeks 1 and 2; increase to 1.2 mg/kg/day div BID for weeks 3 and 4; increase as needed by 1.2 mg/kg/day every 1–2 weeks; maintenance: 5–15 mg/kg/day div BID; max: 400 mg/day div BID > 12 yr: Immediate release: Initial: 25 mg/day for weeks 1 and 2; increase to 50 mg/day for weeks 3 and 4; increase as needed by 50 mg/day every 1–2 weeks; maintenance: 225–375 mg/day div BID With valproic acid–containing regimens: 25 mg QOD for weeks 1 and 2; increase to 25 mg/day for weeks 3 and 4; increase as needed by 25–50 mg/day every 1–2 weeks; maintenance: 100–400 mg/day div in one or two doses; for patients with lamotrigine and valproic acid alone: maintenance dose: 100–200 mg/day With enzyme-inducing regimens, without valproic acid: Initial: 50 mg/day for weeks 1 and 2; increase to 100 mg/day div BID for weeks 3 and 4; increase as needed by 100 mg/day every 1–2 weeks; maintenance: 300–500 mg/day div BID; doses up to 700 mg/day have been used Converting to ER formulation: The daily dose of immediate release should total the initial daily dose of ER. Adjust dose in renal and hepatic impairment.	Tablet, chewable/dispersible tablet, ER tablet, ODT, ext suspension	Boxed warning: Rash (more common in pediatric population, 0.8%; usually occurs within 8 weeks of initiation and resolves after withdrawal; also more common with concomitant valproate) Drowsiness, diplopia, dizziness, headache, insomnia, tiredness, fever (associated with a rash as part of a hypersensitivity syndrome), agitation, confusion, hallucinations, myoclonus	Carbamazepine and phenytoin may increase lamotrigine metabolism, Phenobarbital may decrease lamotrigine levels; valproic acid may increase lamotrigine levels

Levetiracetam (Keppra, Keppra XR)	Calcium channel	4–15 yr: Initial: 10 mg/kg/dose BID, inc by 10 mg/kg/dose every 2 weeks; max: 30 mg/kg/dose BID *Clinically, doses > 80 mg/kg/day are used. ≥ 16 yr (PO/IV): immediate release: 500 mg BID, increase by 500 mg/dose every 2 weeks; max: 1500 mg BID; ER: 1000 mg once daily, increase by 1000 mg/day every 2 weeks; max: 3000 mg/day IV daily dose = PO daily dose Adjust dose in renal impairment.	Injection, solution, tablet, ER tablet	Most common: Dizziness, somnolence, behavior/ personality changes, irritability, hostility, nervousness, accidental injury, asthenia; others: psychotic symptoms, insomnia, emotional lability, ataxia, tremor, headache, nausea	Not cytochrome-dependent
Oxcarbazepine (Trileptal)	Sodium and calcium channels	2–16 yr (adjunctive): < 20 kg: Initiate at 16–20 mg/kg/day div BID; > 20 kg: Initiate at 8–10 mg/kg/day div BID; max: < 20 kg: 600 mg/day, 20–29 kg: 900 mg/day, 29.1–39 kg: 1200 mg/day, > 39 kg: 1800 mg/day 4–16 yr (monotherapy): 8–10 mg/kg/day div BID; increase by 5 mg/kg/day every third day; maintenance: ranges from 600 to 2100 mg/day by weight > 16 yr (adjunctive): Initial: 300 mg BID, increase by 600 mg/day weekly; maintenance: 1200 mg/day div BID, may increase, most patients do not tolerate 2400 mg/day (CNS) > 16 yr (monotherapy): Initial: 300 mg BID; increase by 300 mg/day weekly; maintenance: 1200 mg/day div BID Adjust dose in renal impairment.	Suspension, tablet	More common: Somnolence, dizziness, diplopia, headache, nausea, vomiting; others: rash, ataxia, confusion, cognitive changes (difficulty concentrating, speech or language issues), SIADH	Strong 3A4 inducer, weak 2C19 inhibitor
Phenobarbital	Calcium channel, $GABA_A$ receptor	Maintenance: < 1 yr: 5–8 mg/kg/day div in one or two doses; 1–5 yr: 6–8 mg/kg/day div in one or two doses; 5–12 yr; 3–6 mg/kg/day div in one or two doses; > 12 yr: 1–3 mg/kg/day or 50–100 mg 2 or 3 times/day Adjust dose in renal and hepatic impairment. Therapeutic level: 15–30 mcg/mL Toxic: > 40 mcg/mL	Elixir, injection, tablet, ext suspension	Concentration-related effects: 35–80 mcg/mL: slowness, ataxia, nystagmus; 65–117 mcg/mL: coma with reflexes; > 100 mcg/mL: coma without reflexes Drowsiness, lethargy, mental depression, allergic skin reactions and hyperkinesia, paradoxical responses (hyperactivity, agitation)	Minor 2C9, 2E1, and major 2C19 substrate; strong 1A2, 2A6, 2B6, 2C8, 2C9, 3A4 inducer
Phenytoin (Dilantin, Dilantin-125, Phenytek)	Sodium channel	Loading dose (IV/PO): 15–20 mg/kg/dose Neonates: Initial: 5 mg/kg/day div BID; maintenance: 5–8 mg/kg/day div BID, some patients require TID dosing Infants/children: 5 mg/kg/day div in two or three doses; maintenance: 6 months to 3 yr: 8–10 mg/kg/day; 4–6 yr: 7.5–9 mg/kg/day; 7–9 yr: 7–8 mg/kg/day; 10–16 yr: 6–7 mg/kg/day, > 16 yr: 300 mg/day or 4–6 mg/kg/day in two or three doses	ER capsule, injection, suspension, chewable tablet	Boxed warning: Administer IV phenytoin slowly: not to exceed 1–3 mg/kg/minute in neonates, 50 mg/minute in adults; hypotension occurs with rapid administration Concentration-related effects: > 20 mcg/mL: far lateral nystagmus; > 30 mcg/mL: 45 degree lateral gaze nystagmus, ataxia; > 40 mcg/mL: decreased mental activity; > 100 mcg/mL: death	Major 2C9, 2C19 and minor 3A4 substrate; strong 2B6, 2C8, 2C9, 2C19, 3A4 inducer

(continued)

Table 2. Characteristics of Anticonvulsants (References 3, 10, 22, 24–26) *(continued)*

Anticonvulsant Generic (trade name)	Molecular Target	Pediatric Dosing/Therapeutic Levels	Dosage Formulations	Adverse Effects (Pediatrics Focused)	CYP Drug Interactions
		*~92-mg base phenytoin (suspension/chewable tablet) = 100 mg of phenytoin sodium *For obese patients, loading dose should be based on adjusted body weight, and maintenance dose should be based on ideal body weight.		Hypersensitivity reactions including rash. Common effects: Drowsiness, ataxia, slurred speech (dose related); coarsening of facial features, gingival hyperplasia, hirsutism (rare but with chronic use); anemias (these usually respond to folic acid); motor twitching, dyskinesias (rare), tremor (rare), mental confusion	
Pregabalin (Lyrica)	Calcium channel	Adult: Initial: 150 mg/day in two or three doses, titrate as needed; max: 600 mg/day Adjust dose in renal impairment.	Capsule	Dizziness, somnolence, ataxia, weight gain, headache, blurred vision (adult data)	Not cytochrome-dependent
Rufinamide (Banzel)	Sodium channel	≥ 4 yr: Initial: 10 mg/kg/day div BID; increase by 10 mg/kg/day QOD; maintenance: 45 mg/kg/day or 3200 mg/day div BID (whichever is lower) If taking valproic acid: initial dose: < 10 mg/kg/day Adults: Initial: 400–800 mg/day div BID; increase by 400–800 mg/day every 2 days; max: 3200 mg/day div BID If taking valproic acid: initial dose: < 400 mg/day Adjust dose in hepatic impairment.	Tablet, suspension, ext suspension	QT-interval shortening (dose-dependent), headache, somnolence, fatigue, dizziness, vomiting	Weak 2E1 inhibitor; weak 3A4 inducer; valproic acid may increase rufinamide levels; carbamazepine, phenobarbital, phenytoin, and primidone may decrease rufinamide levels; rufinamide may increase phenobarbital and phenytoin levels
Tiagabine (Gabitril)	GABA transporter	12–18 yr: With enzyme-inducing regimens: 4 mg/day for week 1; 4 mg BID for week 2; then increase by 4–8 mg/day; max: 32 mg/day in two to four doses Without enzyme-inducing regimen: Lower doses are required Adjust dose in hepatic impairment.	Tablet, ext suspension	Dizziness, tiredness, nervousness (nonspecific), tremor, concentration difficulties, depressed mood	Major 3A4 substrate
Topiramate (Topamax)	Sodium channel, $GABA_A$ and glutamate receptors, weak carbonic Anhydrase inhibitor	2–16 yr (adjunctive): Initial: 25 mg/day or 1–3 mg/kg/day, increase by 1–3 mg/kg/day every 1–2 weeks; max: 5–9 mg/kg/day div BID ≥ 17 yr: Initial: 25 mg/day or BID for 1 week; increase by 25–50 mg/week; maintenance: 100–200 mg/day. Doses > 1600 mg not studied ≥ 10 yr (monotherapy): Initial: 25 mg BID, increase by 50 mg/day weekly, up to 100 mg BID for week 4; may then increase by 100 mg/day weekly; max: 200 mg BID Adjust dose in renal and hepatic impairment.	Sprinkle capsule, tablet, ext suspension	Headache, somnolence, dizziness, paresthesia, oligohidrosis, hyperthermia, weight loss (dose-dependent), behavior problems, difficulty with memory and concentration/ attention, metabolic acidosis (chronic use may lead to decreased growth rates, nephrolithiasis, osteomalacia) Secondary acute angle-closure glaucoma or acute myopia—may present as painful red eye (rare and usually occurs within 1 month of initiation)	Weak 2C19 inhibitor; weak 3A4 inducer

Valproic acid (Depacon, Depakene)	$GABA_A$ and NMDA receptors	Children and adults: Initial: 15 mg/kg/day; increase by 5–10 mg/kg/day weekly to therapeutic levels, administered in two to four doses/day; max: 60 mg/kg/day Adjust dose in hemodialysis and hepatic impairment—see warnings Therapeutic levels; 50–100 mcg/mL, efficacy may improve with higher levels, but toxicity can also occur	Capsule, sprinkle capsule, injection, solution, syrup, delayed-release tablet, ER tablet	Boxed warning: May cause teratogenic effects (neural tube defects), hepatic failure in children (< 2 years considerable risk), pancreatitis Occasional: Sedation and tremor; transient hair loss (may be dose related—regrowth normally begins within 6 months); weight gain; gastric disorders (initiation of treatment); hyperactivity, aggression and behavioral deterioration (occasional); transient increase in liver enzymes is common, especially at therapy initiation; hyperammonemia; amenorrhea and irregular periods	Minor 2A6, 2B6, 2C9, 2C19, 2E1 substrate; weak 2C9, 2C19, 2D6, 3A4 inhibitor; weak 2A6 inducer
Vigabatrin (Sabril)	GABA transaminase	Restricted access to medication per REMS program, available from SHARE program 1 month to 2 yr: Initial: 50 mg/kg/day div BID; increase by 25–50 mg/kg/day every 3 days; max: 150 mg/kg/day Adjust dose in renal impairment.	Powder for solution, tablet	Boxed warning: Permanent vision loss in infants, children, and adults (visual field defects) Very common: Somnolence, excitation, agitation; common: nausea, aggression, irritability, depression; fever, vomiting	May decrease phenytoin levels
Zonisamide (Zonegran)	Sodium and calcium channels, weak carbonic anhydrase inhibitor	Infants and children: Initial: 1–2 mg/kg/day div BID, increase by 0.5–1 mg/kg/day every 2 weeks; maintenance dose: 5–8 mg/kg/day; max for infantile spasms: 10–13 mg/kg/day in clinical studies ≥ 16 yr: Initial: 100 mg/day; increase to 200 mg/day after week 2; may increase by 100 mg/day every 2 weeks; if no evidence of increased response, > 400 mg/day in one or two doses Adjust dose in renal and hepatic impairment. Note: Zonisamide should not be used in patients with a sulfonamide allergy.	Capsule, ext suspension	Somnolence, dizziness, oligohidrosis, hyperthermia, metabolic acidosis (chronic may lead to decreased growth rates, rash, SJS, nephrolithiasis, osteomalacia), anorexia	Minor 2C19 and major 3A4 substrate

BID = twice daily; CNS = central nervous system; CYP = cytochrome P450; div = divided; ER = extended release; ext = extemporaneous; GABA = γ-aminobutyric acid; inc = increase; IV = intravenous; max = maximum; LGS = Lennox-Gastaut syndrome; NMDA = *N*-methyl-D-aspartate; ODT = oral disintegrating tablet; PO = by mouth; QID = four times/day; QOD: every other day; REMS = Risk Evaluation and Mitigation Strategies; SHARE = Support, Help, and Resources for Epilepsy; SIADH = syndrome of inappropriate secretion of antidiuretic hormone; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; TID = three times/day; yr = years; XR = extended release.
Reference 35.

lasts. Valproate, propofol, levetiracetam, and medically induced comas with pentobarbital or midazolam have all been used for refractory status epilepticus (References 20, 31). Intravenous valproate and levetiracetam are increasing in use because of safety profiles. Propofol should be used with caution, especially if long-term use is warranted, because of the irreversible propofol infusion syndrome seen in children (hemodynamic instability [hypotension, hyperkalemia, cardiac failure, renal failure], lipidemia, rhabdomyolysis, and severe metabolic acidosis) (References 20, 22). It is generally associated with high-dose, prolonged infusions (greater than 5 mg/kg/hour for more than 48 hours). Monitoring of electrolytes, organ function, and creatine phosphokinase is warranted with propofol infusions. Pentobarbital infusions were found effective in 74% to 100% of refractory status cases in one study (Reference 33). Pentobarbital can be rapidly titrated, but prolonged infusions result in slower elimination because of accumulation in fat stores. Adverse effects such as immunosuppression (high doses) and hypotension resulting in decreased cardiac contractility requiring inotropes may be seen. Pentobarbital contains propylene glycol as a vehicle, and toxicity can result in metabolic acidosis and renal toxicity. Midazolam is the preferred benzodiazepine for continuous infusion because of its short half-life, easy titration, and lack of propylene glycol, which is found in intravenous lorazepam. Some studies have shown midazolam to be less efficacious than other options, but the other options tend to have more adverse effects. All patients placed into a medically induced coma should be intubated, provided respiratory support, and monitored by EEG. Hypotension, which is common, should be observed in these patients. A lack of well-controlled studies with these medications limits the ability to state that that one medication is superior to another.

Syndromes

Many syndromes are treated with specific agents. Infantile spasms with or without a West syndrome diagnosis are primarily treated with adrenocorticotropic hormone or vigabatrin as the first-line agent, with high-dose prednisone as an alternative (Reference 15). Valproic acid, lamotrigine, topiramate, and zonisamide also have been used. Lennox-Gastaut syndrome usually requires several concomitant anticonvulsants to reduce the number of seizure episodes. Typically, valproic acid, felbamate, topiramate, lamotrigine, and zonisamide are options in these patients (Reference 1). Carbamazepine is the anticonvulsant of choice for benign rolandic epilepsy. Juvenile myoclonic epilepsy is commonly treated with valproic acid, but lamotrigine, topiramate, levetiracetam, and zonisamide are alternatives.

Febrile Seizures

Clinical trials have shown that antipyretics administered in a schedule or on an as-needed method are not effective in preventing a febrile seizure or the recurrence of febrile seizures (Reference 16). Simple febrile seizures are typically not treated with anticonvulsants. Many scheduled anticonvulsants have been tried for febrile seizures, but adverse effects or lack of efficacy limits their use; thus, they are not recommended (Reference 16). Carbamazepine and phenytoin have not shown efficacy (Reference 1). Adverse effects have limited phenobarbital (cognitive and behavioral adverse effects) and valproic acid (hepatotoxicity and pancreatitis) (Reference 1). Diazepam has been successfully used intermittently once a fever occurs, but sedation and irritability were reported (Reference 12). Thus, the American Academy of Pediatrics does not recommend continuous or intermittent anticonvulsant therapy for patients with one or more simple febrile seizures (Reference 16). However, anticonvulsants may be considered in patients with complex (atypical) febrile seizures or with neurologic abnormalities.

Monitoring of Therapy

Therapeutic Outcomes

Patients with epilepsy should be assessed and monitored by pediatric neurologists. The frequency of follow-up will depend on the patient, type of seizures, and control of episodes. In general, therapeutic outcomes for patients with seizures or epilepsy include a decrease in the frequency of seizures, with a goal to be seizure free. Patients should experience an improved quality of life and be free of the adverse effects of medication.

Withdrawal of pharmacologic therapy is a decision to be made by the health care providers, patient, and family. Withdrawal may be considered if the patient is seizure free for 2–5 years (mean: 3.5 years) while taking anticonvulsants, has a single type of partial or primary generalized tonic-clonic seizure, has the EEG normalized with treatment, and has a normal IQ and neurologic examination (Reference 34). Children who meet these criteria have a 69% chance of successfully remaining off pharmacotherapy (Reference 34). If patients meet the criteria to attempt to discontinue pharmacotherapy, the medications must be tapered down slowly for several months (Reference 3). Abrupt discontinuation of medications is not recommended unless the patient is experiencing a severe adverse effect. If patients are taking more than one anticonvulsant, one medication will be tapered down gradually first, and when off the first medication, the second medication will be tapered.

While tapering the regimen, if a patient experiences a seizure, the medication should be increased to the previous dose on which the patient did not have a seizure, and withdrawal of the medication should not occur.

Toxicity

Toxicities and adverse effects vary by medication. A few key adverse effects that affect all anticonvulsants will be briefly discussed in this section. Table 2 lists the adverse effects of anticonvulsants that are usually seen in the pediatric population. This is not an inclusive list; thus, consult a drug information resource and literature for a complete list of adverse effects in children and adults. Adverse effects from medications used in status epilepticus are provided in the above treatment section.

Serum drug monitoring continues to be important with respect to the first-generation anticonvulsants because specific levels correspond to efficacy and toxicity in patients. Therapeutic drug serum concentrations are listed in Table 2. Of note, the targeted therapeutic range may be higher than the normal range if a patient is considered resistant to therapy or placed in a drug-induced coma (phenobarbital). However, the second-generation anticonvulsants, when studied, have not shown that serum levels correspond to efficacy or adverse effects. Serum levels are typically not recommended to be drawn for patients taking these medications, but they may be used to verify adherence.

Some anticonvulsants have a drug interaction with oral contraceptive medications (Reference 19). Topiramate, at doses of greater than 200 mg/day; oxcarbazepine; and rufinamide can decrease serum concentrations of ethinyl estradiol. Carbamazepine, phenobarbital, and phenytoin also decrease the estrogen concentrations because of cytochrome P450 drug interactions. Oral contraceptives can also result in a decrease in lamotrigine serum concentrations. Patients of childbearing potential should be notified of these interactions and educated on pregnancy risks.

Although several anticonvulsants are teratogenic, sometimes the benefit of using an anticonvulsant may outweigh the risk. Pregnancy registries are available for patients taking any anticonvulsant medication. Patients may enroll themselves, and all health care providers should educate their patients on using these registries. The FDA pregnancy ratings for anticonvulsants have been known to change as information on fetal effects have been determined. Childbearing women who take anticonvulsants should also supplement with folic acid to prevent birth defects.

In 2008, anticonvulsant labeling changed to include a warning for increased risk of suicidal thoughts or behavior in patients taking these medications (Reference 35). A pooled analysis of 199 trials (monotherapy and adjunctive) showed an incidence rate of 0.43% in treated patients compared with 0.24% in those on placebo and an occurrence in 1 in every 530 patients treated. The risk was seen as early as 1 week after initiating the anticonvulsant and continued throughout the trials (most lasting 24 weeks or less). The FDA has required all manufacturers to develop a medication guide to be provided to patients who are prescribed any of these medications.

Vitamin D supplementation is warranted for patients taking chronic anticonvulsants that are hepatic inducers (Reference 19). Vitamin D levels should be evaluated every 2–5 years in these patients (Reference 3).

Future Therapies

Newer anticonvulsants are generally approved for use in adults first; then, studies may be formally completed or case reports may document the effects in children. Several anticonvulsant chemicals are in trials evaluating efficacy and safety; however, not all chemical entities will be successful enough to make it to the market for patient use.

Conclusions

Seizures and epilepsy are a common pediatric disease state. Various types of seizures and etiologies exist and are the initial guidance for determining treatment options in patients. Not all seizures, epilepsy, or epileptic syndromes will require pharmacologic treatment. However, most patients will be prescribed an anticonvulsant. Anticonvulsants should be used for treatment while balancing the risks and benefits of efficacy and adverse effects. Most patients will be successfully treated with one anticonvulsant, but some patients will be classified as treatment-resistant. In general, therapy should be initiated slowly, and monitoring is required for every patient. The priority in treating seizures and epilepsy is to improve the patient's quality of life.

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CHAPTER 27

Migraines

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Learning Objectives

1. Recognize signs and symptoms of migraines in children.
2. List nonpharmacologic treatment options for migraines.
3. Select appropriate pharmacologic treatment options for migraines.
4. Understand the use of prophylactic drugs for migraines in children.

Abbreviations in This Chapter

AAN	American Academy of Neurology
DHE	Dihydroergotamine
ED	Emergency department
IHS	International Headache Society
PedMIDAS	Pediatric Migraine Disability Assessment Score
PedsQL	Pediatric Quality of Life

Introduction

Headaches are the third leading cause of emergency department (ED) referrals and rank in the top 5 health problems of children (References 1, 2). Headaches, diagnosable in children from young ages to adolescents, may disrupt school or social time. Migraine, a type of primary headache, commonly occurs in the pediatric population and is a chronic condition characterized by acute, recurrent, episodic attacks (Reference 3). Migraine characteristics and long-term prognosis vary among patients. Most adults who have migraines also experienced them during childhood (Reference 4). A child with migraine headaches should be assessed carefully to ensure a correct diagnosis. Optimal migraine management includes the use of both nonpharmacologic and pharmacologic therapies. Migraines appearing in childhood can be a chronic and debilitating disease; thus, appropriate diagnosis and management are warranted.

Epidemiology

The prevalence of migraines in the pediatric population is 3% in children aged 2–7 years, 4% to 11% in children 7–11 years, and 8% to 23% in children 11 years and older (Reference 5). In children, migraine without aura is more than twice as common as migraine with aura. Migraine without aura occurs in more than 60% of children with headaches, whereas migraine with aura occurs in 18% of children (Reference 6). Thirteen percent of children experience both migraines with and without aura. Boys younger than 7 years have a higher prevalence of migraines than girls. The rate of migraine headaches is equal between boys and girls age 7–11 years (Reference 7). Girls tend to have a higher prevalence of migraine headaches than boys do after adolescence. However, boys tend to show an earlier peak onset of migraines at age 7 years, whereas girls have a peak onset at 11 years.

Etiology

Pathophysiology

Several theories exist regarding the pathophysiology of migraines; however, the exact pathophysiology is not clearly understood. Mechanisms include the following: intracerebral arterial vasoconstriction/vasodilation, neuronal dysfunction, activation of the trigeminovascular system, and unknown causes. The intracerebral arterial theory encompasses that during the aura, cerebral vasoconstriction occurs with a reactive extracranial vasodilation, resulting in a headache. Now, scientists believe that it is not simply a vascular mechanism but that other pathways are involved as well, such as neuronal dysfunction and trigeminal sensitization. Neuronal dysfunction is thought to be a depressed cortical spreading of electrical activity that corresponds to the symptoms associated with the presence of the aura (Reference 8). Voltage-gated P/Q-type calcium channels that release glutamate are also involved in the depressed cortical spreading.

Migraines are also thought to be caused by meningeal and blood vessel nociceptor stimulation with central pain modulation (Reference 8). When the trigeminal sensory neurons are activated, substance P, calcitonin gene–related peptide, and neurokinin A are released, resulting in dilation of the blood vessel wall, plasma protein extravasation, and platelet activation. The nerve fibers become more sensitive because of this neurogenic inflammation, resulting in the migraine pain. Conduction along the trigeminovascular fibers transmits signals to higher cortical pain centers. Repeated signaling produces a sensitization of central sensory neurons, resulting in hyperalgesia.

Biologic changes have also been reported because elevated interleukin 1 alpha and tumor necrosis factor have been identified in children with migraines (Reference 9). Decreased coenzyme Q_{10} levels have also been seen in patients with migraines. Furthermore, theories regarding allodynia (pain caused by a stimulus that typically does not evoke pain) are undergoing assessment in children. Patients who experience allodynia during migraines have shown altered responses to treatment (Reference 9). A better understanding of the mechanisms can lead to improved treatment options for patients.

Several comorbid diseases exist with migraines: obesity, epilepsy, sleep disorders, asthma and allergic conditions, and psychological or emotional disease states (Reference 9). Specific mechanisms regarding how the disease state affects migraine development are unknown, but common neurologic pathways are hypothesized. It is also thought that the stress of dealing with multiple disease states can trigger migraines.

Genetic Basis

Genetics plays a large role in migraines. When both parents of a child are interviewed about a history of migraines, 90% will confirm that one or the other has a history of migraines (Reference 10). When only one parent is questioned, a history of migraines occurs in 80%, typically in the mother. Of adult patients with migraines, 50% will have at least one child with migraines. Specific genes are undergoing evaluation to understand the genetic role of migraines and better establish this relationship.

Risk Factors for Disease

Several known triggers and risk factors for migraine exist. Changes in sleep patterns, specific foods, stress, and the menstrual cycle can all exacerbate or be causative factors for a migraine. An attack may be triggered by changes in sleep patterns, such as when a child stays up late or all night to study for an examination. Only 20% of patients have a food trigger related to migraines (Reference 6). Caffeine consumption and hunger are associated with risk of migraines (Reference 6). During times of stress or during a relaxing period after stress, a migraine may occur. These associated attacks tend to occur during school or right after work (Reference 10). Stress from school can be a trigger for pediatric patients because the associated psychological factors and feelings (phobias or anxiety) affect headache frequency (Reference 9). In addition to stress, hormonal levels can be implicated in the onset of migraines. The decline in estrogen hormones during the menstrual cycle is proposed to be a triggering event for menstrual migraines (Reference 10). Oral contraceptives may increase the intensity and frequency of migraine attacks. More frequent attacks generally occur around mid-cycle. Head trauma caused by competitive sports or accidental injury may also cause a migraine, but the specific mechanisms are unknown. Studies have also shown that female, obese children are about 4 times more likely to have headaches than are those with a normal weight (Reference 11).

Clinical Presentation and Diagnosis

The International Headache Society (IHS) classifies migraines in general for adults and children (Reference 12). Migraines are classified as one of six types, as follows: migraine without aura, migraine with aura, childhood periodic syndromes that are commonly precursors of migraine, retinal migraine, complications of migraine, and probable migraine. Some of these classifications have subcategories. The International Classification of Headache Disorders provides specific definitions and diagnosis criteria for each migraine type and subtype (Reference 12). This chapter will primarily focus on migraine without aura. In the diagnosis of migraines, it is important to rule out secondary causes of migraines as well as whether co-primary headaches (e.g., tension-type or cluster headaches) are also present (Reference 3). Examples of secondary causes of migraines include acute viral illness, sinus infection, posttraumatic headache, and intracranial infection (Reference 13).

Signs and Symptoms

The IHS diagnostic criteria specifically describe migraine without aura in children. The IHS criteria include the following traits of children with this type of migraine. The criteria include that children should have at least five or more headaches that (1) last for a duration of 1–72 hours (untreated or unsuccessfully treated), (2) have two of the following characteristics (bilateral or unilateral location, pulsating quality, have moderate or severe pain intensity, or are aggravated by or causing avoidance of routine physical activities), (3) have nausea or vomiting or photophobia or phonophobia (may be inferred from a child's behavior or actions), and (4) not be attributed to another disorder (Reference 12). Migraine attacks can be divided into three phases: prodrome, headache, and postdrome (Reference 6). The prodrome phase can begin as early as 24 hours before the headache and be subtle, causing caregivers not to recognize these symptoms initially. Children may behave differently by experiencing increased thirst, craving particular foods, or refusing food altogether. Children may also have pallor, be inactive, or undergo mood changes. Head pain that follows the initial symptoms is the headache phase. "Throbbing" and "splitting" are commonly used to describe the pain intensity of children's migraines. If there is difficulty understanding children's descriptions, it can be beneficial to ask them to draw their headache. This scheme may help children explain what they are feeling (e.g., ax or

knife pointing to head). As children age, they are able to describe their pain better, and a diagnosis may become clearer. Young children may have difficulty verbally expressing their headache symptoms. Some symptoms may need to be inferred from young children. For example, photophobia may be interpreted when children place a blanket over their head and turn off the light in the room. Headache and vomiting are common symptoms among adults, but children may also have nausea, malaise, and personality changes. Physical activity such as climbing stairs or carrying backpacks can aggravate the pain as well (Reference 6). The duration of migraines in children tends to be shorter than in adults; an episode may last only 1 hour in children but must last at least 4 hours in adults to meet the diagnostic criteria (Reference 12). The duration and frequency of migraines will vary according to the individual child. After a migraine, children most likely are fatigued, but some children experience a paradoxical increase in energy and excitement (Reference 6).

One study of adolescent migraines (n=1,932) revealed that pulsating and unilateral were the most commonly described characteristics of pain presentation (Reference 14). Nausea, phonophobia, and photophobia were experienced by more than 50% of the patients. Younger adolescents had slightly more nausea and vomiting; however, older adolescents described more phonophobia and photophobia. In 88% of the patients, the majority of attacks occurred during the day (from 6 AM to 6 PM) on Monday through Wednesday, and physical activity precipitated the migraine.

In migraine with aura, children have difficulty describing their aura, so again, drawing is a way to express their feelings (Reference 6). The aura occurs less than 30 minutes before the migraine, lasts for 5–20 minutes, and may differ for each migraine episode. Most children experience visual auras such as blurred vision, zigzags, stars, or field defects. Auras may also be sensory-, language-, or motor-related in order of commonality (Reference 15).

Diagnostic Criteria

In preparing to diagnose migraines or headaches in children, information regarding the headache is needed. Specific details include frequency, duration, severity, location on the head, symptoms, and impact of the headache. Box 1 lists example questions that practitioners should ask patients as well as caregivers because caregivers may not always be aware of all the child's symptoms. Practitioners will apply the details of this information to the IHS criteria to see whether the diagnostic criteria are met for migraine without aura. If criteria are not met, other types of migraines or headaches may be evaluated. A Pediatric Migraine Disability Assessment Score (PedMIDAS) or Pediatric Quality of Life Inventory (PedsQL) evaluation should also be completed (References 16, 17). The PedMIDAS is used in children and adolescents and focuses on assessing potential disabilities, the need for prophylactic medication, and response to therapy (Reference 9). The PedsQL evaluation assesses quality of life in the child in a disease-independent manner (Reference 9). A headache pattern should be established by creating a headache calendar and/or diary. Having the patient mark which days a headache occurs, the time of onset, the duration, and the possible precipitating factors can be very helpful. Learning the headache pattern, if one exists, is beneficial for tailoring treatment.

General medical and neurologic examinations may be completed to rule out other presentations such as meningitis and the potential for brain tumors. Patients who present with a normal neurologic examination usually do not warrant neuroimaging (Reference 3). Patients with rapid increases in headache frequency, localized neurologic signs (tingling or numbness, or lack of coordination), or headaches that awaken the patient from sleep (even though 25% of headaches awaken a child) require additional neuroimaging for assistance with diagnosis (References 1, 6).

Course and Prognosis of Disease

By age 25, 25% of adults who had migraines in childhood are migraine free (men more than women) (Reference 10). However, more than 50% of children will still experience headaches at age 50 years. Not all treatment

Box 1. History-taking questions for patients and caregivers with potential headaches.

- When did the headaches start?
- How long do the headaches last?
- How many school days have you missed?
- Does the headache occur in the summer?
- What was the longest period you were headache free?
- How many different types of headaches do you experience?
- Does the headache wake you up at night or start at awakening?
- Is the headache long-term but not restricting, or does it occur sometimes and prevent normal activities?
- What relieves the headache?
- What medications have you tried, how often, and did they work?

Modified from Reference 10. Fenichel GM. Headache. In: Clinical Pediatric Neurology, 5th ed. Philadelphia: Elsevier Saunders, 2005:77–89.

options will be effective in each child with migraines. Quality of life must always be evaluated in patients with migraines because this may be among the first signs that migraines are worsening (Reference 2). Children with migraines experience twice the amount of days lost from school as those without headaches (Reference 10). Regular monitoring of change in activities is imperative in children with migraines to evaluate for worsening of the disease state.

Treatment

Therapy Goals

The American Academy of Neurology (AAN) has set several treatment goals for patients with migraines (Reference 3). The AAN's recommended nonpharmacologic and pharmacologic treatment goals are as follows. (1) Reduce the frequency, severity, and disability of the attack. (2) Decrease patient reliance on poorly tolerated, ineffective, or undesirable short-term pharmacotherapies. (3) Improve the patient's quality of life. (4) Avoid short-term headache medication escalation. (5) Educate, and enable, patients to manage their disease to enhance personal control of their migraine. (6) Lessen headache-related distress and psychological symptoms.

Specifically for an acute attack, the AAN states that the treatment goals are as follows. (1) Treat attacks rapidly and consistently without recurrence. (2) Reestablish the patient's ability to function. (3) Reduce the use of backup and rescue medications. (4) Optimize self-care and decrease the use of subsequent resources. (5) Use therapies that are cost-effective for overall management of care. (6) Ensure that the patient experiences minimal or no adverse events (Reference 3). Rescue medication is defined by the AAN as a medication used at home when other treatment has failed that results in relief of the headache without medical consultation (Reference 3). To improve efficacy, short-term treatment should be administered promptly when a patient determines the onset of a migraine.

Whenever children are experiencing more than one headache per week, the headache is interfering with their activities, or the PedMIDAS score is above 30 showing moderate disability, migraine prophylaxis should be considered (References 9, 18). Other situations that may warrant the use of preventive drugs are when short-term treatment is contraindicated, when disability from migraine occurs despite short-term treatment, when the child is experiencing an uncommon type of migraine, or when the patient prefers such drugs (Reference 19). The goals of prophylactic treatment are to reduce headache frequency to one or two a month and to have the patient experience a decrease in disability (reduce the PedMIDAS score to less than 10 for a period, preferably 4–6 months) (Reference 9).

Migraine therapies can be divided into three areas: nonpharmacologic strategies, short-term treatment, and prophylactic measures.

Nonpharmacologic Therapy

Nonpharmacologic strategies include behavioral therapies such as biofeedback, relaxation techniques, and stress management. Visual and audio biofeedback, such as visualizing a "happy" or relaxing place or telling yourself positive reinforcements, is used to gain physiologic effects. Children are also taught thermal biofeedback, in which they raise the temperature of one of their fingers to shorten a migraine headache. Controlled studies have found positive benefits in this type of therapy (Reference 9). Biofeedback and cognitive behavioral therapies that are designed for a child should be included in the treatment plan (Reference 18). Other therapies are sleep hygiene, regular exercise routines, and dietary modifications. Regular sleep, eating, and exercising regimens are recommended as part of the biobehavioral therapy (Reference 18). Disruptive sleep or a change in sleep patterns are beginning to be recognized in children as having a major impact on migraines. In children, dietary triggers that have been associated with migraines include chocolate, cheese, and citrus fruits (Reference 20). Other food precipitants include monosodium glutamate (a preservative used commonly in Chinese food), aspartame, processed meats, yogurt, and alcohol. If a food is found to be a trigger of migraines, it is recommended that the patient use avoidance techniques. Caffeine is also a culprit in migraine occurrence. In this case, migraines may be caused by caffeine withdrawal or its impact on sleep patterns. Meal skipping can also trigger migraines. This is common in many adolescents who skip breakfast. Strong scents such as perfumes or candles can also precipitate a migraine because smell is a sensory stimulus.

All patients with a diagnosis of migraines can potentially benefit from a nonpharmacologic therapy; however, behavioral and physical interventions are typically used for preventing migraine episodes rather than for alleviating acute symptoms of an attack. Optimal management of acute migraine attacks includes the use of both nonpharmacologic and pharmacologic therapies.

Pharmacologic Therapy

Nonprescription Medication

Acute Attacks

Acetaminophen and ibuprofen are safe and effective for short-term migraine treatment in children, but the AAN provides a higher rating of recommendation for ibuprofen than for acetaminophen (Reference 5). Acetaminophen is typically dosed at 10–15 mg/kg per dose (maximum dose: 1000 mg) every 4–6 hours (not

to exceed five doses in 24 hours, or 3 g daily). For migraines, ibuprofen should be dosed at 7.5–10 mg/kg per dose (maximum dose: 800 mg) every 6–8 hours (maximum daily dose: 2,400 mg) (References 5, 9). Although few studies exist for either drug, ibuprofen has undergone more studies than acetaminophen (Reference 5). Many children experience excellent efficacy results with these nonprescription drugs alone and do not require the use of prescription drugs. No clinical trials regarding the use of other nonprescription drugs in migraines are available. Salicylates, although effective in adults, are usually avoided in children because of the risk of Reye syndrome.

Prophylaxis

Herbal products (e.g., feverfew, butterbur root, coenzyme Q_{10}, magnesium, riboflavin) have been proposed as beneficial for preventing migraines. Their specific mechanisms of actions are unknown; however, deficiencies in coenzyme Q_{10}, magnesium, and riboflavin in patients with migraines have been shown (References 9, 18). Supplementation with butterbur or coenzyme Q_{10} has shown a decrease in headache frequency in children (Reference 18). However, a recent double-blind, randomized, placebo-controlled, crossover trial of coenzyme Q_{10} did not improve headache outcomes in 120 children (Reference 21). In studies, magnesium showed a lack of efficacy versus placebo for prophylaxis of migraines in children, and riboflavin has conflicting evidence regarding its ability to decrease migraine frequency. Feverfew has not been studied in children. Because trials with herbal products are limited, well-designed, larger studies are warranted. Studies evaluating the combination of herbal products are under way. It is important to remember that herbal products are not under the U.S. Food and Drug Administration (FDA) label approvals or regulations, and caution should be exercised if they are used.

Prescription Drugs

Acute Attacks

The serotonin receptor agonists, or "triptans," are the prescription medications primarily used for moderate to severe migraines or for migraines that do not respond to nonprescription drugs (Reference 19). They are selective for the serotonin 5-HT_{1B} and 5-HT_{1D} receptors found on the intracranial blood vessels, central nervous system neurons, and trigeminal nerve endings (Reference 8). Administration of these agents results in vasoconstriction and decreased inflammation in the cranial arteries, inhibition of trigeminal neurons, and interceded transmission in the trigeminal nucleus. The 2004 treatment parameters for acute migraine attacks in children and adolescents stated that nasal sumatriptan was effective and should be considered (Reference 5). Only sumatriptan, rizatriptan, and zolmitriptan were discussed in that guideline because data were limited or lacking at that time (Reference 5). Currently, six of the seven available triptans show efficacy and safety in children (Reference 22). Of the available triptan data, nasal sumatriptan, oral rizatriptan, orally dissolving and nasal zolmitriptan, and almotriptan have more positive efficacy studies than do others in the triptan class in children. Nasal formulations of sumatriptan and zolmitriptan have provided the strongest efficacy data. In several well-designed studies, oral formulations have not been shown to be better than placebo, but positive clinical data exist, and these dosage forms may be considered for treatment. Almotriptan is the first triptan to obtain an FDA indication in adolescents 12 years and older with migraines lasting 4 hours or more. This approval was based on two studies, one large clinical trial and one very small open-label pilot study, both of which showed tolerability and safety. Naratriptan and eletriptan lack sufficient data to recommend for first- or second-line use in a pediatric patient with migraines. Frovatriptan has only one pharmacokinetic study, limiting its use in the population. Pharmacokinetic data in children and adolescents are similar to those in adults. The triptan class should be considered a first-line short-term treatment option for pediatric patients with migraines who require prescription medication. Although almotriptan is the only FDA label-approved triptan in pediatrics at this time, other triptans may be used clinically, given the data presented in the primary literature. Specific drug selection may be influenced by the route of administration, matching the pharmacokinetics of the drug with patient symptoms (i.e., longer duration if migraines recur quickly), and the cost of the product. Dosing varies according to medication and dosage form (Table 1). Efficacy from clinical trials of the pediatric population was based on data using one dose; however, most triptan medications that are FDA label approved state that a repeat dose of triptan may be administered 2 hours after the first dose with a maximum of two doses per day. Specifics on maximal daily doses vary according to product. Combining a triptan with a nonprescription medication for migraine relief has not yet been evaluated in children. The combination product of sumatriptan and naproxen sodium is effective and safe in adolescents with migraines. Other combinations of prescription and nonprescription medications for migraine relief have not yet been assessed in pediatrics.

For migraines, the AAN recommends that butalbital- and opioid-containing drugs be limited and carefully monitored if used (Reference 19). Some practitioners avoid narcotics and butalbital products because they have not been formally studied in children or adolescents. They have also been associated with drug-overuse

Table 1. Medication Dosing for Migraines (References 18, 22)

Medication Generic (Brand)	Pediatric Dose Used in Clinical Studies	Maximum Dose per Day
Acetaminophen (Tylenol)	10–15 mg/kg/dose (maximum dose: 1000 mg)	Five doses per day or 3000 mg
Ibuprofen (Advil, Motrin)	7.5–10 mg/kg/dose (maximum dose: 800 mg)	2400 mg
Sumatriptan	Nasal: 5–18 years: 5 mg or 20 mg	40 mg
(Imitrex/Alsuma/Sumavel)	Subcutaneous: 6–18 years: 3–6 mg	12 mg
	Oral: 8–17 years: 25–100 mg	200 mg
Rizatriptan (Maxalt/Maxalt MLT)	Oral tablet: 20–39 kg: 5 mg; > 40 kg: 10 mg	30 mg[a]
	Oral disintegrating: 12–17 years: 5 mg	
Zolmitriptan (Zomig)	Oral: 12–17 years: 2.5 mg, 5 mg, 10 mg	10 mg
	Oral disintegrating: adult: 2.5 mg	
	Nasal: 12–17 years: 5 mg	
Naratriptan (Amerge)	Oral: 12–17 years: 0.25 mg, 1 mg, 2.5 mg	5 mg
Almotriptan (Axert)	Oral: 12–17 years: 6.25–12.5 mg[b]	25 mg
Eletriptan (Relpax)	Oral: 12–17 years: 40 mg	80 mg
Frovatriptan (Frova)	Oral: 12–17 years: 2.5 mg[c]	7.5 mg
Sumatriptan/naproxen (Treximet)	Oral: Adult: sumatriptan 85 mg and naproxen 500 mg (1 tablet)	2 tablets

[a]5 mg daily maximum if on propranolol
[b]FDA approved for 12-17 years
[c]No efficacy studies in pediatrics

headaches and withdrawal; thus, practitioners have limited their use (Reference 8). Adolescents with menstrual-related migraines can benefit from oral contraceptives or progesterone depot injections. An initial case series reported symptom benefit in six female adolescents who were administered botulinum toxin type A for migraines, but adverse effects such as burning sensations at injection sites, blurred vision, and mild ptosis did occur (Reference 23). Additional studies regarding the use of this drug in children with migraines are warranted.

Antiemetics are also used for migraine symptoms. It is believed that antiemetics with dopaminergic mechanisms (prochlorperazine, promethazine, and metoclopramide) may treat the underlying pathophysiology as well, not just the associated nausea or vomiting. One retrospective review of intravenous prochlorperazine found only a 14% failure rate in children with severe migraines in the ED setting (Reference 24). All patients were administered diphenhydramine to prevent akathisia. Caution must be used with promethazine because it has a warning of respiratory depression in children (contraindicated in children younger than 2 years) and may cause extrapyramidal adverse effects. Metoclopramide also can cause extrapyramidal symptoms. Ondansetron, a serotonin ($5\text{-}HT_3$) receptor antagonist, has become a popular antiemetic in children because of its safer adverse effect profile versus the phenothiazine derivatives. Ondansetron is available as an oral disintegrating tablet or as soluble film, and it may be administered intravenously when nausea or vomiting is a concern. Efficacy trials of pediatric migraine headaches with ondansetron are unavailable.

During acute attacks, alternative routes of medication (e.g., subcutaneous, intranasal, rectal) should be used when migraines are associated with severe nausea or vomiting in the patient (Reference 3). Counseling on short-term therapies is important, regardless of the specific drug prescribed. First, all patients should take the drug as soon as possible after the first symptom or when the headache begins. Next, using the drug appropriately (e.g., correct dose and interval) is important to reduce the potential of overuse or adverse effects. Finally, the patient should keep the drug available in a location where he or she usually has headaches. This may be at school, after-school day care, or work. Short-term treatment should not be used for more than three headaches per week (Reference 18).

Some patients with migraines will seek treatment in the ED because of failed home management. The antidopaminergic drugs as well as intravenous ketorolac have shown benefit in the ED setting (Reference 18). Prochlorperazine has shown superiority to ketorolac in a head-to-head study of children 5–18 years old in the ED setting (Reference 25). Combining these two drug classes has resulted in increased efficacy (Reference 18). About 6% to 7% of patients with migraines do not obtain relief from medications in the ED, so they are admitted to an inpatient service for migraines (Reference 18). A migraine that is a debilitating attack lasting more than 72 hours is termed *status migrainosus* (Reference 12). This type of migraine is severe in intensity and is usually treated in the inpatient setting (References 12, 18). Intravenous dihydroergotamine (DHE) may be used in a low- or high-dose protocol to stop an intractable migraine. Administered every 8 hours until the headache ceases or until the maximal dose (15 mg) is reached, DHE was found to be 97% effective in headache improvement and 77% effective in headache relief in a small study of 32 children and adolescents (Reference 26). Intravenous valproic acid has also been used for this type of migraine. These are not FDA label-approved uses in children, but case reports and open-label studies have shown benefit (Reference 18).

Prophylaxis

Most children do not require prophylactic medications for migraines. Currently, none of the drugs marketed in the United States are FDA label approved for prophylaxis use in children. In Europe, flunarizine, a calcium channel blocker, is approved because of several studies showing its efficacy (Reference 18). The AAN also supports the use of flunarizine, but availability limits its use (Reference 5). Current treatment options for prophylaxis in children include cyproheptadine, amitriptyline, propranolol, valproic acid, and topiramate (Table 2). Cyproheptadine has antiserotonergic effects and may have calcium antagonistic characteristics (Reference 18). One study has shown it to be comparable to

Table 2. Medications Used for Migraine Prophylaxis (References 18, 27)

Drug	Dose	Maximum Dose per Day	Contraindications/ Boxed Warnings	Drug Interactions
Antihistamine				
Cyproheptadine	0.25–1.5 mg/kg or 4–8 mg TID	24 mg	MAO inhibitors, acute asthma attack, GI tract obstructions, stenosing peptic ulcer	Decrease effects of SSRIs; enhance CNS depressant effects
Antidepressant				
Amitriptyline	10–50 mg daily at bedtime		MAO inhibitors; U.S. boxed warning: worsening of depression or suicidal ideations in children with depression	Major 2D6 and minor 1A2, 2B6, 2C19, 2C9, 3A4 substrate; weak inhibitor of 1A2, 2C19, 2C9, 2D6, and 2E1
β-Blocker				
Propranolol	2–4 mg/kg/day or 10–40 mg TID	4 mg/kg/day or 120 mg	Asthma, hyperactive lung disease, sinus bradycardia, heart block greater than first degree, sick sinus syndrome	Major 1A2, 2D6 and minor 2C19, 3A4 substrate; weak inhibitor of 1A2, 2D6, P-glycoprotein
Anticonvulsants				
Valproic acid (VPA)	20–40 mg/kg/day	1000 mg	VPA: Liver disease or dysfunction, U.S. boxed warnings: hepatic failure (children < 2 years at greatest risk), pancreatitis	VPA: Minor 2A6, 2B6, 2C9, 2C19, 2E1 substrate. Weak inhibitor of 2C9, 2C19, 2D6, 3A4. Weak inducer of 2A6.
Topiramate (TOP)	1–10 mg/kg/day (usual 50 mg BID)	200 mg	TOP: None	TOP: Weak inhibitor of 2C19; weak to moderate inducer of 3A4

BID = two times/day; CNS = central nervous system; GI = gastrointestinal; MAO = monoamine oxidase; SSRI = selective serotonin reuptake inhibitor; TID = three times/day.

amitriptyline and propranolol. Amitriptyline has been used in children since the early 1980s, but dosing has varied (Reference 18). Propranolol has shown mixed results in its efficacy of preventing migraines (Reference 5). Both valproic acid and topiramate are effective in decreasing migraine severity, duration, frequency, and PedMIDAS scores (Reference 18). However, studies also exist showing no difference from placebo (Reference 28). Yet these two anticonvulsants have been studied the most regarding migraine prophylaxis in children. Very small, uncontrolled studies of levetiracetam and zonisamide have shown a decrease in migraine frequency, but larger studies are warranted before recommending their use (Reference 28).

When selecting preventive therapy, consider the patient's comorbid disease states and potential drug interactions. For example, although β-blockers may be considered in children with anxiety, they should be avoided in patients with asthma or diabetes. Valproic acid or topiramate may be considered in a child with epilepsy or bipolar disorder. Drug interactions between short-term and prophylactic therapy should be evaluated, as should interactions with the patient's long-term medications. Propranolol is a major substrate of cytochrome P450 (CYP) 1A2 and CYP2D6 and weakly inhibits CYP1A2 and CYP2D6 as well as P-glycoprotein. Valproic acid also is known for drug interactions within the CYP system. All medications should be initiated at a low dose and titrated to response while monitoring for adverse effects.

Monitoring of Therapy

Therapeutic Outcomes

The treatment goals of the AAN should continue to be evaluated on follow-up with patients. Quality of life and impact on activities should be monitored for improvement. All medications used for acute attacks have a potential risk of causing rebound of the headache, and children with migraines have a higher risk of developing analgesic overuse headaches (Reference 18). Patients, in general, should not be using pharmacologic treatments more than three times/week. If so, this may be a predictor that prophylaxis therapy is warranted. Prophylaxis should be initiated for a specific period. If headaches are controlled at 6 months of treatment, discontinue or taper the drug (Reference 19). Weaning during summertime may be done to see how school-aged children are doing with respect to migraine frequency. Some patients, however, may need long-term prophylaxis for longer periods.

Toxicity

In general, treatment options for an acute migraine attacks are tolerated well. Ibuprofen and acetaminophen are commonly used for other indications, and most patients have previous experience with these drugs. The triptan class has been evaluated for safety in children, and adverse effects are similar to those seen in the adult population. Chest tightness, jaw tightness, or asthenia may be described by the child, but they are self-limiting (Reference 18). Taste disturbances are reported with nasal formulations, and injection site reactions are seen with subcutaneous injections (Reference 22). Serotonin syndrome is also a concern with triptan use. Educating patients regarding signs and symptoms is important so that they are aware of this possibility. The pharmacist should also evaluate the patient's medication profile for potential drug interactions. Contraindications for all triptans include ischemic heart disease, uncontrolled hypertension, basilar or hemiplegic migraine, and administration within 24 hours of ergotamine derivatives or other serotonin agonists. Most triptan studies in the pediatric population excluded patients with congenital heart disease and other cerebral vascular diseases, so caution is warranted in those patients. Adverse effects of DHE include nausea and vomiting (prophylaxis medications are administered in the DHE protocols), chest tightness, hives, facial flushing, and increased blood pressure (Reference 26). Ergotamines should not be used during pregnancy.

Adverse effects with prophylactic medications vary according to product. In general, concerns with weight gain exist with cyproheptadine and valproic acid. Drowsiness occurs with cyproheptadine and amitriptyline. Fatigue is associated with propranolol, and β-blockers should be avoided in patients with asthma, depression, or diabetes. Topiramate causes cognitive changes such as impaired concentration, emotional instability, and paresthesia. Adverse effects must be monitored to ensure that quality of life is not decreasing because of the preventive drug.

Future Therapies

Future treatment options tend to be focused on the trigeminovascular system. Currently, oral calcitonin gene–related peptide receptor antagonists and glutamate receptor inhibitors are being evaluated for migraine treatment and prophylaxis, respectively. Several drugs are being studied for new formulations or devices to administer the drug in needle-free devices, patches, or inhaled forms. After showing efficacy, these drugs will likely gain approval for use in the adult population first. It is unknown whether pediatric approval will be

sought. Several triptans are currently under investigation for their effectiveness in children (Reference 29). A few trials are also investigating topiramate for use in preventing migraines in children 12 years and older.

Conclusions

Migraines occur commonly in the pediatric population. They can be debilitating and affect the school, social, and home life of a child. Appropriate diagnosis and close follow-up with monitoring are recommended for all patients. Nonpharmacologic and pharmacologic therapies should be used in children with a diagnosis of migraines to improve symptoms and increase quality of life. Biofeedback, relaxation techniques, and stress management are nonpharmacologic therapies to consider in children with migraines. Ibuprofen or acetaminophen is an appropriate first-line short-term nonprescription treatment option, with the triptan class considered a first-line prescription treatment option for children and adolescents. Several medications (e.g., propranolol, amitriptyline, valproic acid, topiramate) have been used for prophylaxis therapy in children. The understanding of this disease state, assessment, and treatment will continue to change as they are further studied. Migraine management will continue to expand as evidence is discovered regarding new short-term and preventive drugs as well as nonpharmacologic strategies.

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CHAPTER 28

Autism Spectrum Disorders

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Learning Objectives

1. Explain the clinical presentation and diagnostic criteria for autism spectrum disorder (ASD).
2. Discuss the application and efficacy of pharmacotherapeutic interventions for symptom-specific treatment and the limitations of pharmacotherapy in ASD.
3. Recommend and monitor pharmacotherapy for ASD for therapeutic outcomes and adverse drug effects, together with considerations of possible comorbid conditions.

Abbreviations in This Chapter

ABC-I	Aberrant Behavior Checklist—Irritability subscale
ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
CARS	Childhood Autism Rating Scale
CGI	Clinical Global Impression Scale
DSM	Diagnostic and Statistical Manual for Mental Disorders
EPS	Extrapyramidal symptoms
IDEA	Individuals with Disabilities Education Act
OCD	Obsessive-compulsive disorder
PANDAS	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection
PDD	Pervasive developmental disorder
PDD-NOS	Pervasive developmental disorder–not otherwise specified
SSRI	Selective serotonin reuptake inhibitor

Introduction

Pervasive developmental disorders (PDDs) often present considerable problems and challenges for patients, families, caregivers, and health care providers. The five PDDs recognized in the *Diagnostic and Statistical Manual for Mental Disorders* (*DSM-IV-TR*) are Asperger's disorder, autistic disorder, childhood disintegrative disorder, Rett's disorder, and pervasive developmental disorder-not otherwise specified (PDD-NOS) (Reference 1). Autism spectrum disorders (ASDs) are a subset of PDDs that include autistic disorder, Asperger's disorder, and PDD-NOS (see Figure 1). This chapter will focus on autistic disorder as the predominant ASD.

In 1943, Dr. Kanner described children who withdrew, disregarded people, avoided eye contact, lacked social awareness, had limited language, displayed stereotyped motor movements, and showed a preservation of sameness as having a disorder called early infantile autism (References 2, 3). At the time, Dr. Kanner proposed that autism resulted from an inborn inability to form loving relationships with other people and described the parents of these children as cold and detached. Today, although the general behavioral description of the disorder has not changed significantly, the proposed causes of autism are now believed to be more neurobiologic in etiology, though they are still not definitively known (Reference 3).

The most significant clinical features of a child with an ASD often include qualitative impairments in the major domains of (1) social interaction or reciprocity, (2) communication and language, and (3) repetitive, restricted, or stereotypic behaviors. Other problematic and maladaptive behaviors that may prompt the use of pharmacotherapy include irritability, tantrums, aggression, and attention-deficit/hyperactivity symptoms (Reference 1).

Epidemiology

The prevalence of ASDs has been a matter of debate in recent years. Some estimate the numbers to be 1 or 2 per 1000, whereas other reports estimate the prevalence to be as high as 1 or 2 per 100 (References 4–12). The average is reported to be 6 or 7 per 1000 children for the three ASDs combined (Reference 8). It is thought that the increased prevalence of ASDs is because of the increase in awareness through media coverage and the application of diagnostic criteria (Reference 8). Criteria for infantile autism were provided in the *DSM-III*, but the criteria have changed through the years, which may have affected how the disorder is identified. Another event that may have affected the diagnosis rate of ASDs is the passage of the Individuals with Disabilities Education Act (IDEA) in 1990 (Reference 8). With

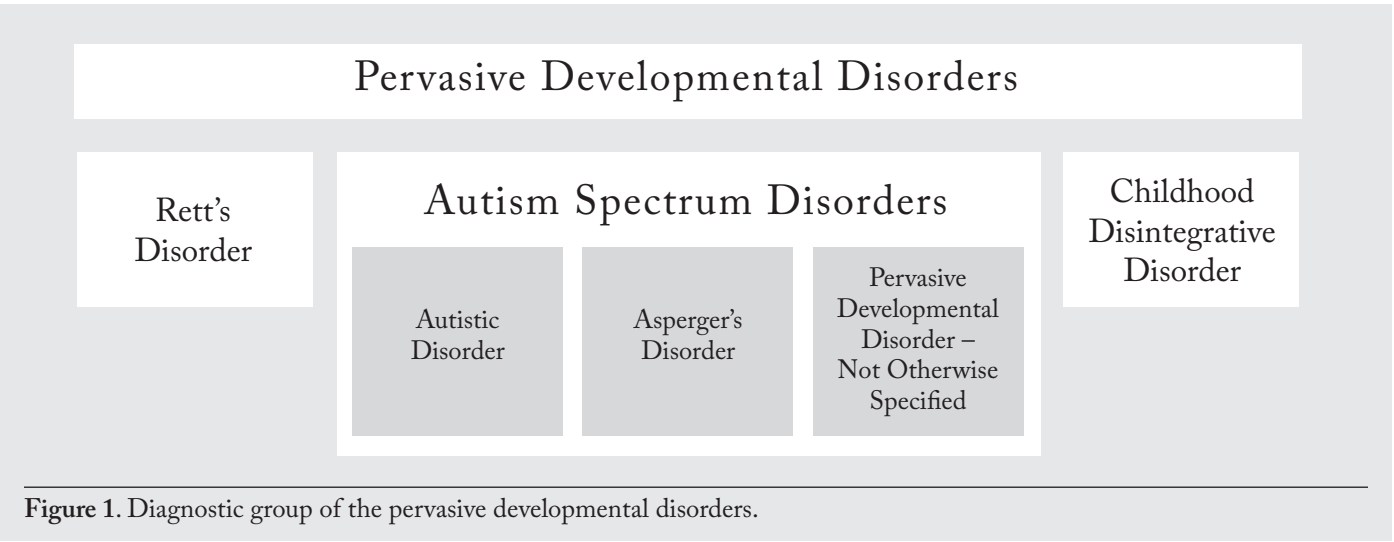


Figure 1. Diagnostic group of the pervasive developmental disorders.

IDEA, services could be billed for ASDs. Until IDEA was passed, autistic disorder did not become a diagnosis in which children became eligible to receive special education services (Reference 8).

The reported ratio of males to females with ASDs in the United States is approximately 4.5:1 (References 5, 8). There may be racial differences in prevalence, with non-Hispanic white children identified more often than non-Hispanic black children or Hispanic children (References 5, 13). The gender, racial, and ethnic differences may be culturally based, with less reporting in certain groups. Other countries may also have differences in prevalence because of the reporting of neuropsychiatric disorders or limited diagnostic and treatment resources. No evidence exists for a socioeconomic boundary, with similar rates across social status and cultures (Reference 8). Children having siblings with an ASD also have a higher likelihood of receiving a diagnosis of an ASD, with the risk being approximately 10-fold (References 8, 14–18).

Etiology and Pathophysiology

The etiology of ASDs is unknown. The earliest proposed cause of autistic disorder—dysfunctional attachment as a result of parenting style—is no longer accepted. Today, the ASDs are thought to have a heterogeneous etiology that is neurobiologically based with a complex genetic, and therefore possibly heritable, component. Genetic mutations are being evaluated in research, but no specific causes have been identified (References 8, 14–21). The discovery of copy number variations, and the clinical and behavioral similarities of ASDs to other syndromes with recognized genetic deletions or mutations reinforce the proposed genetic abnormalities that may underlie ASDs (References 8, 19, 20). Syndromes such as fragile X syndrome (gene = *FMR1*), Angelman syndrome (gene = *UBE3A*), and *Tuberous sclerosis* (genes = *TSC1* and *TSC2)* are examples of syndromes with recognized genetic mutations that also have behaviors similar to ASDs (References 8, 17, 22).

Determining the biochemical markers for the ASDs (e.g., abnormal neurotransmitter levels) in both the periphery and central cerebrospinal fluid has been extensively researched; however, data are inconclusive. A dysfunction in serotonin has the strongest support for explaining the behaviors associated with ASDs, though evidence is inconclusive (References 23–25). Earlier hypotheses that endogenous opioids or norepinephrine was implicated in the pathology of ASDs are not consistently supported (Reference 24). Dopamine dysfunction is still a target of research, given the efficacy of the antipsychotics, with both older and newer atypical agents demonstrating the ability to reduce ASD symptoms (References 23, 24). Various hormones and neuropeptides (e.g., cortisol, oxytocin, vasopressin) have also been suggested as factors in the etiology of ASDs; however, these hypotheses have minimal support (References 8, 23, 25).

Claims put forth in the early 1990s—subsequently determined to have been based on fraudulent data (and retracted by the publisher of the data, *The Lancet*)—that vaccinations were related to the development of autistic disorder have been disproved by several investigations (References 8, 26–30). Despite the evidence that vaccinations do not contribute to ASD, many parents continue to believe that vaccinations caused their child to develop ASD (References 30, 31). One hypothesis for the relationship between vaccines and ASDs was that some vaccines contained thimerosal as a preservative; however, this compound has been removed, or greatly reduced to only trace amounts, from most vaccine products. Although this action by the pharmaceutical industry took place about 10 years ago, ASD rates have not decreased since then, supporting the lack of relationship

between thimerosal exposure and ASD (References 30, 32). Exposure to heavy metals such as lead and mercury remains a potential causal factor in some cases of neurodevelopmental deficits (References 8, 33). Abnormal immune responses have also been proposed to be related to ASDs. This theory may still be connected to vaccine exposure as a form of immune system activation, though further research is needed in this area before accepting the existence of a connection between vaccinations or infections and abnormal immune responses leading to ASD (References 8, 34, 35).

Neuroimaging studies indicate the involvement, and possible dysfunction, of various areas of the brain, including the cortical, subcortical, and limbic regions, which may reflect early pathology (References 8, 36–40). Increased head circumference in early years (accelerated growth in the first year) will approach normal to below normal after childhood (deceleration) (Reference 39). Together with increased head size in 20% to 30% of children with ASDs, imaging reveals a general increased brain volume (References 8, 36–39). Certain neuronal cells (e.g., Purkinje cells in the cerebellum, forebrain cells, frontal and temporal lobe cortical mini-column cells, and cells in the area of Broca) are smaller (References 8, 37–39). Brainstem abnormalities have also been observed (References 38, 39). One explanation for the impairments in empathy, imitation, and language could be a dysfunction in mirror neurons (Reference 40).

Other proposed risk factors for ASD include maternal and fetal exposure to teratogenic medications, selective serotonin reuptake inhibitor (SSRI) antidepressants, neurotoxins, smoking, alcohol, infection, and prenatal malnutrition (References 8, 25, 33, 41, 42). These environmental factors may act as modulators to the expression of preexisting genetic factors. Older parents (older than 35–40 years) have a higher risk of having children with ASDs, which may be related to spontaneous genetic mutations, such as a copy number variant related to age (References 43–45).

Clinical Presentation and Diagnosis

The signs of ASDs are generally present before 3 years of age. The American Academy of Neurology and the Child Neurology Society suggest being aware of the following "red flags," which are indicators to evaluate further and immediately for ASDs (Reference 46):

- No babbling, pointing, or other gesture by 12 months
- No single words by 16 months
- No two-word spontaneous (not echolalic) phrases by 24 months
- Loss of language or social skills at any age

The three core domains in most ASDs are social interaction, communication, and stereotypic or repetitive behaviors. The diagnosis of autistic disorder requires the presence of qualitative impairments and deficits in (1) two or more aspects of social interaction and reciprocity, (2) one or more aspects of communication and language use and development, and (3) the presence of one or more behaviors demonstrating restricted, repetitive, and stereotyped patterns, such as rocking, hand flapping when excited, bizarre gestures (hands to ears), or posturing, which are considered purposeless, though may actually be attempts to self-stimulate or avoid aversive stimuli. Children with Asperger's disorder often present with impairments in only social interaction and repetitive, restrictive, or stereotypic behaviors, while language skills remain unimpaired (References 1, 8). The *DSM-IV-TR* criteria for autistic disorder are provided in Box 1. The *DSM-IV-TR* criteria, for a comparison to Asperger's disorder, are provided in Box 2. Children not meeting the specific criteria for either autistic disorder or Asperger's disorder because they have an atypical presentation or lack enough symptoms can be given the PDD-NOS diagnosis if other conditions have been ruled out (References 1, 8, 46).

Cognitive deficits that may qualify as mental retardation (IQ of 70 or less) are often present in children with ASDs (References 1, 8). Also seen commonly in this population are EEG (electroencephalogram) abnormalities and epilepsy (Reference 47). Many children with ASDs also present with comorbidities or associated symptoms of attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression, together with the co-occurring maladaptive behaviors and symptoms of aggression, irritability, tantrums, poor impulse control, and self-injurious behavior (References 1–3, 8, 46). A clinical syndrome that requires more research into etiology and treatment and that may be rarely encountered with some clinical presentations similar to ASD is the group of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS), in which the child may demonstrate new-onset stereotypic or ritualistic and obsessive-compulsive behaviors. However, PANDAS can reverse with time and antibiotic treatment whereas ASD does not (References 48, 49).

Some children with ASD may present with gastrointestinal problems such as constipation or diarrhea, whereas others may have difficulties with sleep patterns. Appropriate evaluation of these problems is recommended to rule out other reversible causes of the aforementioned problems, and appropriate symptomatic management is recommended. The clinician should also consider that the patient's behavioral changes may be secondary to disturbances in sleep or gastrointestinal distress (Reference 50). Although pharmacotherapy is

Box 1. Diagnostic criteria for autistic disorder.

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):
   1. qualitative impairment in social interaction, as manifested by at least two of the following:
      a. marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
      b. failure to develop peer relationships appropriate to developmental level
      c. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
      d. lack of social or emotional reciprocity
   2. qualitative impairments in communication as manifested by at least one of the following:
      a. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
      b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
      c. stereotyped and repetitive use of language or idiosyncratic language
      d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
   3. restricted, repetitive, and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
      a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
      b. apparently inflexible adherence to specific, nonfunctional routines or rituals
      c. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
      d. persistent preoccupation with parts of objects
B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play
C. The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.

sometimes used for the gastrointestinal or sleep disturbances in ASD, these issues should be addressed and treated according to recommended pediatric guidelines for such symptoms. Some of the psychotropic medications selected for disturbed behaviors in this population will carry the adverse effects of sleep disturbances (sedation or insomnia) and gastrointestinal disturbances (constipation or diarrhea), and these issues should be considered during pharmacotherapy selection and monitoring.

Box 2. Diagnostic criteria for Asperger's disorder.

A. Qualitative impairment in social interaction, as manifested by at least two of the following:
   1. marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
   2. failure to develop peer relationships appropriate to developmental level
   3. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
   4. lack of social or emotional reciprocity
B. Restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
   1. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
   2. apparently inflexible adherence to specific, nonfunctional routines or rituals
   3. stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
   4. persistent preoccupation with parts of objects
C. The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.
D. There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).
E. There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.
F. Criteria are not met for another specific pervasive developmental disorder or schizophrenia.

Evaluations to aid in diagnosing ASDs include neuropsychological, medical, speech-language, audiologic, neurologic, and laboratory analysis to rule out other, better-explained diagnoses and environmental factors such as heavy metal exposure (e.g., lead) (References 1, 8, 46).

Treatment

Treatment Goals

The goal of treatment for any ASD is not to cure or prevent. Pharmacologic treatment strategies target a core aspect of the ASD (e.g., a disruptive behavior) that is interfering with the individual's ability to participate in other treatments designed to achieve maximum functional ability. For example, if a child with ASD is verbally and physically aggressive toward the occupational or speech-language therapist, progress is impeded until the aggression is addressed. These disruptive, or even dangerous, behaviors may also be placing them at risk of harming themselves or others. When a child with ASD demonstrates disruptive, irritable, aggressive, or agitated behaviors that do not respond to nonpharmacologic behavioral interventions, targeted pharmacotherapy may be warranted (Figure 2) (References 50, 51). A clinically meaningful reduction in the problematic behaviors of irritability, aggression, and self-injury is the desired

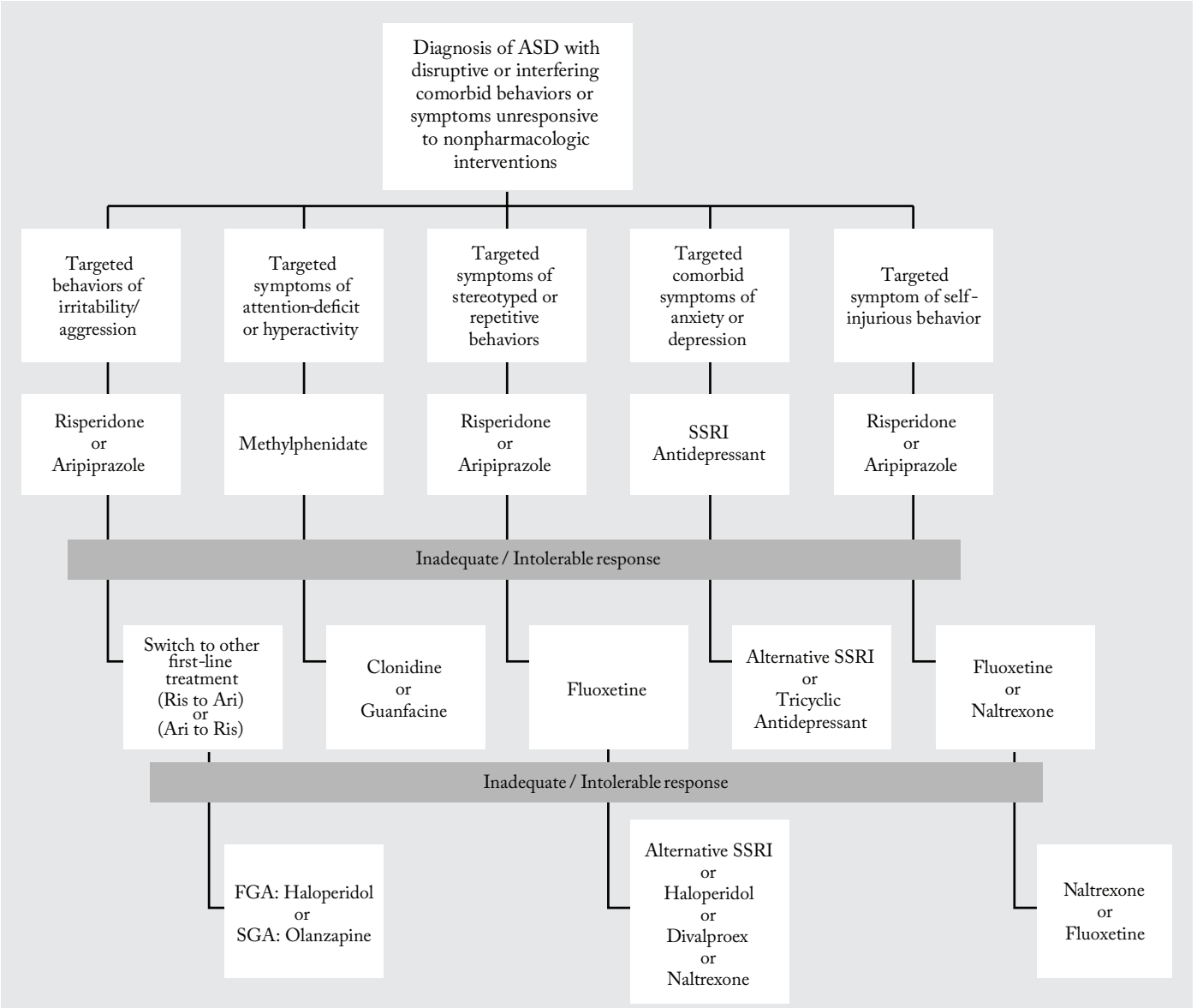


Figure 2. Pharmacologic treatment algorithm for ASD.

ARI = Aripiprazole; ASD = autism spectrum disorder; FGA = first-generation antipsychotic; RIS = Risperidone; SGA = second-generation antipsychotic; SSRI = selective serotonin reuptake inhibitor.

outcome so that the individual can then engage in the nonpharmacologic treatments intended to improve his or her overall functioning in all the affected domains and identified deficits (Reference 50).

Nonpharmacologic Treatments for ASD

Nonpharmacologic treatments for ASD should be implemented in a coordinated manner before pharmacologic treatment (Reference 50). Therapies that may be beneficial in the management of a child with ASD include occupational therapy, physical therapy, educational interventions, behavioral therapy (e.g., applied behavior analysis), speech-language therapy, and possibly diet modification in those who are responsive to such an intervention (References 52–54). Common dietary changes include reducing or eliminating dairy protein intake (casein-free) and certain protein-containing cereals (gluten-free) (Reference 53). Dietary modifications in research provide inconsistent results; however, many parents of children with ASD will attempt this intervention, with mixed outcomes, before more costly or medically warranted interventions. Given the case-based lay and medical literature of benefit and the mixed results of dietary modification in formal research studies, this practice of dietary modification continues, and if it successfully reduces some of the problematic behaviors or symptoms in a particular child with ASD so that the child may engage in other treatments, it also then serves to empower and offer a level of control by the family and caregivers regarding the child's total treatment.

Approximately 50% of parents of children with ASDs use complementary and alternative treatments, despite the lack of evidence for their efficacy. Such treatments include the use of dietary supplements (e.g., vitamins B and C, omega-3 fatty acids, magnesium, melatonin), acupuncture, sensory integration, and aromatherapy (References 50, 54, 55).

Pharmacotherapy of ASD

Pharmacotherapy is best used to allow the child to better engage in his or her treatment plans such as speech-language plans, occupational therapy plans, or those that are educationally, behaviorally, or socially oriented for maximum benefit to the child with an ASD. The impairments in social interaction and communication are generally unresponsive to pharmacotherapy. Even maladaptive behavioral problems should be managed without medications, if possible, with psychotropic medications being reserved for moderate to severe problems with specific behaviors such as irritability and aggression (References 50, 56, 57). Pharmacotherapeutic interventions may also be used for a comorbid symptom of the disorder such as inattention, hyperactivity, or repetitive/stereotypic behaviors that are also interfering with the child's overall treatment plan and that are not responding adequately to the nonpharmacologic interventions. Medical treatment of comorbid diagnoses such as epilepsy, gastrointestinal problems, or sleep disorders may also be required in many children with ASD (Reference 50).

Steps to determine the need for, and implementation of, pharmacotherapy for ASD should include the following (adapted and modified from References 50, 51):

- Identify and perform a baseline assessment of target behaviors through multiple sources (e.g., parents, teachers), together with factors and triggers modifying the behaviors.
- Assess the degree of interference with functioning and consider using rating scales and clinical judgment (by the clinician) to establish baseline functioning both before the intervention and at follow-up to determine positive and negative outcomes.
- Determine the efficacy achieved with behavioral interventions and other psychosocial supports and education.
- Identify potential medical factors through physical assessment and testing that may be causing or exacerbating the target behavior(s) (e.g., pain, gastrointestinal discomfort, sleep disorders, menstruation).
- Consider psychotropic medication given the evidence that the target symptoms are interfering with learning/academic progress, socialization, and health/safety (self and others) or the patient's quality of life and that there was a suboptimal response to nonpharmacologic interventions.
- Choose a medication on the basis of known efficacy for the specific target symptoms, its potential adverse effects, formulations available, dosing schedule, and need for laboratory or other monitoring (e.g., electrocardiographic).
- Acquire informed consent from the parent/guardian and, when possible, from the patient.
- Establish a plan for monitoring and following up all treatment outcomes and the desired or expected timeframe for such outcomes, including laboratory and physical monitoring for changes in weight, glucose, lipids, and other potential laboratory values affected by the chosen medication.
- If outcomes are less than desired or expected, and adequate dosing and length of treatment was achieved, then consider alternative treatment options, including switching to another agent or augmentation with a different medication.

Table 1. Pharmacotherapy Options for ASD

	Target Symptoms with Level of Evidence[a]						
Medication	**Core Domains**				**Associated Behaviors**		
	Social Interaction	**C/L**	**S/RB**	**Irritability/Aggression**	**Attention**	**Hyperactivity**	**SIB**
Antipsychotics							
Risperidone	B		A	A	B	B	B/C
Aripiprazole			A	A	B	B	B/C
Haloperidol	C		C	A		B	
Olanzapine				B			
Quetiapine				C			
Ziprasidone				C			
SSRIs							
Fluoxetine			B				C
Fluvoxamine			D				D
Citalopram			D				D
Clomipramine			C	C/D			C/D
α1-RAs							
Clonidine			C/D	C		C	
Guanfacine			C/D	C		C	
Psychostimulants							
Amphetamine				F		F	
Methylphenidate					C	B	
Others							
Naltrexone	C/D		B/C	C		C	C
Divalproex			B/C				
Atomoxetine						B	

[a]A = Multiple DBPC studies with positive efficacy; B = one DBPC study (moderate to large N); with positive efficacy (or two small N studies); C = open-label studies with positive efficacy; D = questionable efficacy with limiting ADRs/positive efficacy through case reports/series; F = negative efficacy studies with problematic ADRs.
ADR = adverse drug event; ASD = autism spectrum disorder; C/L = communication/language impairments; DBPC = double-blind, placebo-controlled (study); RA = receptor agonist; SIB = self-injurious behavior; S/RB = stereotypy/repetitive behaviors; SSRI = selective serotonin reuptake inhibitor.

- If the patient has responded favorably for the past 6–12 months, consider tapering and discontinuing treatment to reassess the need for pharmacotherapy.

The pharmacologic management of children with ASDs includes many medications that are indicated for other disorders and are not U.S. Food and Drug Administration (FDA) approved for autistic disorder or any other PDD (see Table 1). Only two antipsychotics are FDA approved with established efficacy and safety for irritability associated with autistic disorder (References 58–69). Research indicates that most subjects receiving pharmacotherapy for irritability can have some clinically recognized improvement. However, because a target symptom may be similar to symptoms encountered in other disorders for which these agents have established efficacy, or that are co-occurring because of another diagnosed disorder, the use of certain medications (e.g., SSRIs, psychostimulants) is accepted practice. Published research also supports the use of certain medications for targeted symptom management. These behaviors or symptoms may include repetitive or stereotyped behaviors that resemble the symptoms of obsessions and compulsions and therefore may respond to the medications approved for obsessive-compulsive

disorder (OCD), such as some of the SSRIs (References 70, 71). Symptoms of inattention and hyperactivity may respond to prescribed psychostimulant medications, though these agents may exacerbate irritability and agitation (Reference 72). In addition, other agents used in attention-deficit disorder and ADHD (e.g., clonidine, guanfacine) may be beneficial for certain targeted symptoms such as hyperactivity and aggression (References 73–76).

The use of various medications for ASD management has been increasing during the past 2 decades. A 1995 study indicated approximately 30% of children with ASD were receiving a psychotropic medication. More recently, a study of children with ASD in a Medicaid population sample indicated that up to 56% of the children with ASD were receiving at least one psychotropic medication, and 20% of the children were receiving three or more medications concurrently. Antipsychotic medications were reported as the most commonly prescribed class of psychotropics in this population, with antidepressants and psychostimulants being the second and third most commonly used, respectively (References 77–79).

Antipsychotics

Historically, first-generation antipsychotics have been used in the management of maladaptive behaviors associated with ASD. Although not approved for treating ASD, haloperidol was the most commonly used and studied agent before the atypical antipsychotics were developed. And although haloperidol has been shown to be efficacious in treating the irritability, aggression, and even stereotypes associated with ASD in several small studies, its risk of extrapyramidal adverse effects such as dystonias, tremors, and the potentially irreversible tardive dyskinesia significantly limits its use today (References 80–85). In 40 autistic children 2–7 years of age, haloperidol was effective in reducing behavioral symptoms and producing general clinical improvement (Reference 80). Based on published research, the optimal dose may be no more than 1–2 mg/day. In addition to extrapyramidal symptoms (EPS), other adverse effects including increased appetite, weight gain, and sedation may also limit its use in this population. Sustained and higher-than-average prolactin levels secondary to antipsychotic use may have untoward effects on development in both females and males (References 60, 86). Clinically, manifestations of high prolactin levels can include gynecomastia, galactorrhea, amenorrhea, and possibly osteoporosis; thus, monitoring for these adverse effects is warranted.

In 2006, risperidone became the first FDA-approved medication for the treatment of irritability associated with autistic disorder in children and adolescents 5–16 years of age. It has well-established efficacy in multiple double-blind, placebo-controlled, and open-label trials (References 50, 58–65). The two principal double-blind, placebo-controlled trials used for FDA approval established the efficacy of risperidone using the outcome measurements of the Clinical Global Impression Scale (CGI) and the Aberrant Behavior Checklist (ABC) (References 58, 61, 62, 66). Up to 75% of subjects in the trials had a CGI score of either 1 ("very much improved") or 2 ("much improved") compared with only 11% of subjects receiving placebo. At least 50% of the subjects had a reduction in the ABC-Irritability subscale (ABC-I) of at least 25%. The mean reduction in the ABC-I for risperidone was 57% compared with the mean reduction in the placebo group of 14% (Reference 61). The maladaptive behaviors of irritability, aggression, tantrums, and self-injury are the principal targets when using risperidone; however, research indicates that other symptoms, such as hyperactivity and stereotypy, may improve as well. The core domains of communication impairment and problems with social interaction are not considered principal targets of pharmacotherapy with risperidone, though these symptoms may occasionally improve with pharmacotherapy. The manufacturer-recommended dosage range is 0.25–3 mg/day, with higher doses sometimes needed for individuals weighing more than 45 kg. The recommended starting dose and range are based on weight (0.01–0.06 mg/kg/day), with 0.25 mg/day for children weighing less than 20 kg and 0.5 mg/day for children weighing 20 kg or more. Titration up to the effective dosage should take place every 2 weeks in increments of 0.25–0.5 mg/day, with a target dose of 0.5 mg/day for children weighing less than 20 kg and 1 mg/day for children weighing 20 kg or more (References 65, 66). Commonly reported adverse effects that were reported during the clinical trials include fatigue (42%), somnolence (67%), increased appetite (49%), weight gain (5%), hypersalivation (22%), and EPS (7% to 12%) such as dystonias, tremors, and dyskinesias (References 58, 61, 62, 64, 66). Increases in prolactin levels have been observed during clinical trials and should be monitored for in children and adolescents receiving risperidone, together with possible clinical manifestations of hyperprolactinemia such as gynecomastia and galactorrhea (References 60, 86).

In 2009, aripiprazole became the second FDA approved agent for the treatment of irritability associated with autistic disorder in children and adolescents 6–17 years of age (Reference 67). Like risperidone, the approval was based on two studies, with results indicating that aripiprazole was superior to placebo in reducing the symptom of irritability associated with autistic disorder in children and adolescents, 6–17 years of age, by at least 25% as well as in achieving a "much-improved" or "very much-improved" score on the CGI for more than 50% of the subjects taking medication compared

with only 16% of the subjects receiving placebo who achieved a "much-improved" or "very much-improved" rating. The mean reduction in the ABC-I for aripiprazole was 44% compared with the mean reduction in the placebo group of 16% (References 68, 69). The recommended treatment dosage range is 2–15 mg/day. A once-daily dose of 2 mg is the recommended starting dose; 5–10 mg/day is the recommended treatment dose; and 15 mg/day is the maximum recommended dose for children 6–17 years of age (Reference 67). Common adverse events reported during the trials included sedation (21%), fatigue (17%), vomiting (14%), tremor (10%), hypersalivation (9%), decreased appetite (7%), dizziness, and EPS (6%). Although comparison data are lacking, aripiprazole appears to have a lower risk of significant weight gain than other atypical antipsychotic agents that may be used in ASD (References 66, 67, 87, 88).

Other atypical antipsychotic agents have also been researched in ASD. In one placebo-controlled, double-blind study, olanzapine was shown to have positive efficacy for the treatment of aggression and irritability in children and adolescents with a PDD (n=11 [6: autistic disorder; 1: Asperger disorder; 4: PDD-NOS], 6–14 years of age) (Reference 89). Clozapine, ziprasidone, and quetiapine have been evaluated in small open-label studies or case reports, with modest efficacy in reducing irritability, aggression, and tantrums reported (References 90–92). Further research is required with these agents and with the more recently approved atypical antipsychotics (paliperidone, asenapine, iloperidone, lurasidone) to establish their potential roles in treating children with ASD.

On the basis of early experiences with antipsychotic medications in ASD and the established efficacy and approval of risperidone and aripiprazole, these two agents should be considered first-line treatment; after treatment failure or the inability to use one of these two agents because of intolerability, other antipsychotics should be considered.

Antidepressants

Stereotypic behaviors present with symptoms similar to obsessions and compulsions. The SSRIs have been studied and used in clinical practice for the repetitive behaviors in ASD; however, their overall efficacy appears inconsistent. Medications such as clomipramine, fluoxetine, sertraline, escitalopram, and fluvoxamine have been evaluated for their ability to reduce repetitive behaviors with limited and mixed results (References 70, 71, 93–95). Although fluoxetine has proved to have some efficacy in reducing the repetitive behaviors associated with ASD when using the CY-BOCS (Child-Yale Brown Obsessive Compulsive Scale), agents such as fluvoxamine have shown minimal efficacy in children (References 70, 71, 89).

Other SSRIs such as sertraline and paroxetine have only been studied in case reports and open-label trials, which do not consistently support their use in children with ASD (Reference 71). Citalopram was studied at a mean dose of 16.5 mg/day in a relatively large placebo-controlled, double-blind trial (n=149) of children and adolescents 5–17 years of age with ASD. Citalopram was no different from placebo in clinical outcomes, yet it caused significant adverse events including activation, impulsiveness, hyperactivity, stereotypies, diarrhea, and insomnia (Reference 95). If the decision is made to use an SSRI, the prescriber should consider using agents with established safety and tolerability in children and adolescents from data generated from other approved indications such as OCD or depression. These agents include fluoxetine, sertraline, escitalopram, and fluvoxamine.

Clomipramine, a highly serotonergic tricyclic agent, was the first agent approved in U.S. adults for OCD. Clomipramine has been studied in trials (dosage range 25–250 mg/day; mean 150 mg/day) of both child and adult populations and has shown modest efficacy compared with desipramine (n=24 subjects 6–18 years of age and showing superior efficacy to desipramine) and haloperidol (n=36 subjects 10–36 years of age and showing efficacy similar to haloperidol). The areas of improvement were generally related to obsessive-compulsive behaviors and stereotypies, but they also included reductions in anger and hyperactivity, as well as an overall general improvement, as reflected in the CGI-Improvement Scale of the subjects. However, the tolerability and general adverse effect profile of clomipramine suggest it should be used after other agents such as antipsychotic agents and SSRIs have failed (References 81, 94).

Psychostimulants

For ADHD-like symptoms that accompany ASD, psychostimulants such as methylphenidate have been used with mixed results (References 96–98). The response to psychostimulants in the ASD population may be less than that experienced by someone with ADHD without ASD. In addition, the response to psychostimulants may be better for children with Asperger's disorder than for children with autistic disorder or PDD-NOS (Reference 97). The amphetamines also have limited efficacy data, with no controlled studies since the 1970s, which is before current diagnostic criteria were used. Results indicated minimal benefit with potential adverse effects, including a worsening of ASD symptoms (Reference 50).

Both clonidine and guanfacine were recently FDA approved for ADHD treatment. Both agents have been studied in children and adolescents with ASD with reports of moderate efficacy in reducing symptoms of

stereotypy, hyperactivity, and irritability (References 73–76). Sedation and fatigue are frequent adverse effects of α_2-agonists. Other agents with limited research include divalproex for reducing repetitive behaviors and atomoxetine for effectiveness in reducing hyperactivity (References 99, 100). Naltrexone continues to be questionable in efficacy and utility. Many studies have been done, both open label and placebo controlled, and the results are mixed. Although naltrexone may not be very effective for self-injurious behaviors and social interaction, as originally postulated, it may have some effect on hyperactivity and is generally well tolerated (References 72, 101, 102).

Monitoring of Therapy

Monitoring of ASD in clinical practice is generally through parental and observer reports, together with teacher and other caregiver input. Assessment tools such as the ABC, Childhood Autism Rating Scale (CARS), or CGI are used in research, but not commonly in practice. The ABC-I is a 15-item parent-rated or primary caregiver–rated assessment focusing on agitation, aggression, tantrums, self-injury, and unstable mood with a possible 0–45 score; higher scores indicate greater severity of symptoms. In research, a common outcome goal is achieving at least a 25% reduction in symptoms of irritability compared with baseline. The CARS is a clinician assessment tool to assist with both diagnostics and the monitoring of individuals with ASD. The CARS has 15 items assessing several areas including social interactions and relationships, communication, and behaviors. The CGI is rated (1 = not at all ill up to 7 = extremely ill) for severity or improvement, with 1 = very much improved versus 7 = very much worse, and clinicians generally use these versions in research to provide a simplified and global rating of severity or level of change at baseline and follow-up, respectively (References 103–105).

Specialty-specific outcomes (e.g., speech-language), other than a general improvement from baseline and on follow-up, are both individualized and different, depending on the type of deficits or behaviors being addressed through treatment and the type of treatment or therapy being used (References 8, 50, 51). When the previous scales are used in research, improvements can be observed sometimes within 1 week of treatment; however, an adequate trial of the appropriate medication at the appropriate daily dose may require up to 8 weeks or more before that intervention is declared a success or failure, unless it must be discontinued early because of intolerable adverse effects to the patient. In addition to clinical monitoring for efficacy outcomes, the use of the antipsychotics and other psychotropics warrants the monitoring of laboratory values that assess metabolic parameters such as lipids and glucose control. Prolactin levels should be assessed at baseline and periodically, together with observable manifestations of hyperprolactinemia such as gynecomastia and galactorrhea. Regular monitoring for weight changes in patients taking antipsychotics, psychostimulants, mood stabilizers, and antidepressants is also recommended. Many agents for treating ASD may also cause movement disorders in the form of EPS (dystonic reactions, pseudoparkinsonism, akathisia, tardive dyskinesia), motor tics, or tremors. Consider a baseline assessment of clinical symptoms, laboratory values, and physical parameters, with a follow-up in 1 month; then, provide a quarterly assessment as indicated unless caregiver or patient input or monitoring parameters warrant assessments more frequently.

Pharmacotherapeutic Outcomes

The desired outcomes of pharmacotherapy are best described as reductions in the maladaptive and problematic behaviors so that the child with ASD can then engage in nonpharmacologic treatments such as speech-language therapy or educational treatment plans (Reference 51). The sometimes limited efficacy of the psychotropics discussed in this chapter should be considered, together with their liabilities of adverse effects such as weight gain, sedation, or even the possible worsening of some of the behaviors of ASD. Given that the ASDs are not considered reversible, some children with ASD may require long-term treatment with medications, and the risks of long-term exposure to some of the medications discussed are not well known. Nonpharmacologic interventions should be the first-line treatment with psychotropics held in reserve for more severe cases (References 50, 51). The atypical antipsychotic medications risperidone and aripiprazole, which have been approved for use in autistic disorder, were only approved for use in 2006 and 2009, respectively. Some adverse effects of medications may take years to manifest, such as problems secondary to significant weight gain or the development of tardive dyskinesia with antipsychotics or, yet undetermined, the long-term negative effects with other psychotropics such as the SSRIs or psychostimulants. The type of symptom identified as problematic, disruptive, and thus targeted to be addressed with pharmacotherapy will influence the medication selected. The antipsychotics are best suited for the disruptive behaviors of aggression, irritability, tantrums, and stereotypic/repetitive behaviors. If there is a recognized comorbid attention deficit or hyperactivity, a psychostimulant may be warranted, though caution should be taken not to exacerbate preexisting irritability or agitation. If comorbid anxiety or depression is occurring, an antidepressant that is FDA approved for child and adolescent use is recommended. Self-injurious behaviors may respond not only to antipsychotics, but also

to SSRIs and possibly naltrexone. Some practitioners, who may associate the repetitive behaviors with obsessive-compulsive symptoms, could prescribe an SSRI or clomipramine for said behaviors, given their efficacy for OCD. Again, it is important to consider pharmacotherapy as a targeted, symptomatic treatment approach to assist in the patient's total treatment plan to maximize functioning that may be inhibited by his or her disruptive and aggressive behaviors, thereby making the patient unable to engage in the equally important nonpharmacologic interventions designed to address the other core areas of ASD.

Conclusions

The use of medications to treat the maladaptive behaviors and comorbid symptoms of ASD is a common practice, according to surveys of prescribers and parents (References 77–79). With only two medications currently FDA approved for the treatment of irritability related to autistic disorder, most pharmacologic agents are being used off-label, though with some research supporting their use and, thus, with evidence for their positive benefit in reducing certain behavioral problems. The prescriber should keep in mind, and discuss with the patient's caregivers and family, that pharmacotherapy in ASD is for symptomatic management only. Because improvements in the core features of ASD can be made through other interventions and over time, the need for pharmacotherapy should be reassessed periodically. If the maladaptive and other co-occurring problematic behaviors such as irritability, tantrums, agitation, and hyperactivity are addressed, then ideally, the child with ASD can better engage in the other treatments and therapies that can address the core domains of the ASD and improve overall outcomes.

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CHAPTER 29

Pediatric Bipolar Disorder

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Learning Objectives

1. Describe the etiology and pathophysiology of pediatric bipolar disorder (PBD).
2. Explain the signs and symptoms and diagnostic criteria for bipolar disorder in pediatric patients.
3. Describe the treatment goals of PBD.
4. Evaluate pharmacologic therapy for the treatment of bipolar disorder and determine the best treatment for specific patients, including mood stabilizers, antipsychotics, and adjunctive treatments.
5. Discuss common monitoring parameters for the pharmacologic treatments of bipolar disorder.

Abbreviations in This Chapter

ADHD	Attention-deficit/ hyperactivity disorder
Bipolar disorder NOS	Bipolar disorder not otherwise specified
BMP	Basic metabolic panel
CBC	Complete blood cell count
CYP	Cytochrome P450
DA	Dopamine
DSM-IV TR	Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.)
ECG	Electrocardiogram
FDA	U.S. Food and Drug Administration
GABA	γ-Aminobutyric acid
LFTs	Liver function tests
PBD	Pediatric bipolar disorder

Introduction

Bipolar disorder (or manic depression) is a serious mental illness that includes severe mood fluctuations and changes in behavior. Bipolar disorder differs from major depressive disorder; in bipolar disorder, manic, hypomanic, or mixed mood episodes occur in addition to depressive episodes. The diagnosis of bipolar disorder in children and adolescents remains controversial leading to revised diagnostic criteria discussed below. In fact, many clinicians feel pediatric bipolar disorder is over diagnosed and has become a "catch-all diagnosis" for children with even mild behavior problems. Although bipolar disorder is a lifelong illness, treatments (pharmacologic and nonpharmacologic) are available that can improve functioning and provide short- and long-term mood stabilization. The pharmacologic treatment of bipolar disorder is perhaps even more controversial than the diagnosis. Efficacy and safety of pharmacologic treatments have been questioned by lawmakers and clinicians alike. Many unknowns are present when treating pediatric bipolar disorder with pharmacotherapy and some of these are addressed throughout the chapter.

Epidemiology

Diagnosis of bipolar disorder in children and adolescents has increased in recent years, possibly because of a better recognition of symptoms in this population (Reference 1). Other factors that may contribute to a higher rate of diagnosis include a better understanding of the difference in presentation between children and adults and a greater acceptance of the diagnosis in children (removing the stigma from diagnosis). However, the diagnosis of bipolar disorder in children and adolescents is still controversial. Pediatric bipolar disorder (PBD) is estimated to occur in 1% of children and adolescents, with equal occurrence in boys and girls (Reference 2). In addition, adult patients given a diagnosis of bipolar disorder retrospectively identify symptoms in childhood (Reference 3).

Etiology

Pediatric bipolar disorder is likely the result of a combination of various genetic and biologic abnormalities and environmental stressors or insults. The adult literature has found a genetic association in patients with bipolar disorder and their families. Patients having a first-degree relative with bipolar disorder are 4–6 times more likely to have the illness (Reference 4), and several twin and adoption studies verify this (Reference 5). Neurochemical theories on the pathophysiology of PBD involve the monoaminergic system (serotonin, norepinephrine, and dopamine [DA]), γ-aminobutyric acid (GABA), intracellular secondary messenger system, and neuronal membrane calcium and/or sodium (Reference 6). The

monoamine theory states that an imbalance of the neurotransmitters serotonin (5-HT), norepinephrine, and DA causes mania and depression. Evidence for this theory is that medications that decrease these neurotransmitters (antipsychotics) relieve mania, whereas medications that increase these neurotransmitters (antidepressants) relieve depression. Another, related theory states that a deficiency of GABA or an excess of glutamate may also contribute to mania and depression. This theory is evidenced by the efficacy of certain antiseizure medications, which act to increase GABA or decrease glutamate. The intracellular secondary messenger system and neuronal cations may be important in "kindling," in which the exaggerated and spontaneous firing of neurons occurs because of imbalances in these systems. The kindling theory is similar to the pathophysiology theories in epilepsy and is important in rapid cycling bipolar disorder and mixed states (Reference 7). Kindling theory states that, when patients who are predisposed to bipolar disorder experience stressful life events or take certain medications or illicit substances, the "threshold" at which mood changes occur decreases. Eventually, the decrease in threshold becomes so low that mood episodes begin occurring without any identifiable cause. Evidence for this theory is that many anticonvulsants used in bipolar disorder have efficacy in rapid cycling and mixed states. Other pathophysiologic theories include dysfunctions in the hypothalamic-pituitary-thyroid axis and increased cholinergic tone in the central nervous system (Reference 6). Environmental factors such as psychosocial stress (illicit drug use, family discord, school difficulties, etc.) or changes in the seasons, which disrupt the circadian cycle and the amount of light exposure, also play a role in precipitating manic or depressed episodes (Reference 6).

Clinical Presentation and Diagnosis

Before a diagnosis of mania is made, secondary causes of mania need to be ruled out (Table 1) (References 8, 9). The medical conditions and medications that cause secondary depression appear in the Pediatric Depression chapter. The clinical workup for pediatric patients with suspected bipolar disorder includes a thorough psychiatric interview and mental status examination. Additional information should be obtained, including personal and family psychiatric and medical history and medication history. A questionnaire that helps a clinician diagnose PBD is K-SADS, or the Kiddie-Schedule for Affective Disorders and Schizophrenia (Reference 10). Other tests that can rule out secondary causes of mania include a physical and neurologic examination; laboratory tests such as thyroid function, basic metabolic panel (BMP), urine drug screen, complete blood cell count (CBC), and liver function tests (LFTs); and psychological testing. Brain imaging (computed tomography or magnetic resonance imaging), lumbar puncture, or electroencephalogram may be obtained; however, they are only for ruling out secondary causes, not in the diagnosis of PBD.

Differential diagnosis of PBD includes cyclothymia (hypomania and dysthymia), attention-deficit/hyperactivity disorder (ADHD), posttraumatic stress disorder, pervasive developmental disorders, oppositional defiant disorder, conduct disorder, reactive attachment disorder, and abuse of or withdrawal from recreational drugs. Many of these diagnoses may be common comorbidities as well. For example, ADHD has been described in up to 90% of patients with PBD (References 5, 11). Distinguishing PBD from other diagnoses can be difficult and may take more than one interview with a patient. This difficulty is very apparent when trying to differentiate between PBD and ADHD because their diagnostic criteria have some overlap; however, some guidance exists to help clinicians with the diagnosis. Although patients with ADHD will have short, impulsive bursts of anger because of not reaching a goal, their underlying mood between outbursts is described as "happy" or "angry" but rarely "sad" or "overly elated," as seen in PBD. Patients with PBD tend to have constant irritability that can appear as openly hostile, vicious, or dangerous, which is not present in ADHD. In addition, patients with PBD often have episodes of unpredictable rage and an episodic illness characterized by mood

Table 1. Other Causes of Mania (References 8, 9)

Medical conditions that may cause mania

- Thyroid disorders
- Infections
  - Neurosyphilis, sepsis, encephalitis
  - Central nervous system conditions
- Tumor, seizures, Huntington disease, stroke, lupus, multiple sclerosis, head trauma
- Addison or Cushing disease

Drugs that may cause mania

- Withdrawal from substances of abuse
- Alcohol intoxication
- Antidepressants
- Dopamine agonists
- Hallucinogens
- Steroids
- Thyroid replacement medications
- Caffeine or theophylline
- Pseudoephedrine
- St. John's wort

changes over time. Normally, ADHD does not manifest with changes in mood. Elated mood, grandiosity, flight of ideas, and decreased need for sleep more likely indicate PBD than ADHD (References 5, 12).

The defining characteristic of bipolar disorder is mania or hypomania. Table 2 summarizes the diagnostic criteria for mania and hypomania in the *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed, text rev (DSM-IV TR) (Reference 8). The main difference between hypomania and mania is the level of impairment the patient shows. If the patient is still able to function in everyday life or does not require hospitalization, but still has symptoms consistent with a manic episode, he or she would be given a diagnosis of hypomania. A manic episode is necessary for a diagnosis of bipolar disorder type I, whereas a hypomanic episode with a history of depression indicates bipolar disorder type II. Bipolar disorder not otherwise specified (NOS), however, accounts for a large portion of PBD diagnosis. Bipolar disorder NOS describes patients who may not meet full criteria for bipolar type I or II, but still display signs and symptoms consistent with the diagnosis of bipolar disorder. Many pediatric patients who do not have a classic adult bipolar disorder presentation are given the diagnosis of bipolar disorder NOS. During any mood episode, except for hypomania, a patient may have psychotic symptoms such as hallucinations, delusions, or paranoia. Patients have rapid cycling bipolar disorder when four distinct mood episodes (any combination of depressive, hypomanic, or manic episodes) occur within a year. Although these criteria are for adult patients, they have been extrapolated successfully to the pediatric population. However, there is controversy surrounding whether the adult diagnostic criteria adequately describe or include all the symptoms related to PBD. This controversy has led some clinicians and researchers to use the term *juvenile mania* to describe manic symptoms that do not meet classic adult mania criteria (Reference 5).

For example, adolescents with a diagnosis of bipolar disorder may have a more chronic illness course, which is refractory to treatment, in addition to markedly labile moods. Mixed states (having symptoms of mania and depression in the same episode) and psychotic episodes are also more common in patients receiving a diagnosis in adolescence. Younger children (younger than 12 years) may have a quite different presentation. Mood changes, energy level changes, and behavioral symptoms are often not consistently present, but rather, they wax and wane frequently. Instead of a euphoric or excessively happy mood, younger patients may have irritability, anger, and/or mixed features. Other symptoms of mania that may be more pronounced in younger patients are grandiosity, flight of ideas, and decreased need for sleep. Their long-term prognosis is often worse than that of adults because patients may be refractory to medication (Reference 5).

Depressive symptoms in PBD are similar to adult symptoms, with some exceptions. Many patients experience irritability, which may be mistaken for mania. The occurrence of fatigue, anhedonia, and suicidal ideation should be screened for in patients presenting with irritability to differentiate whether the irritability is caused by mania or depression. Further complicating the diagnosis of depression in patients with PBD is the high incidence of mixed episodes in this population.

Table 2. DSM-IV TR Mania and Hypomania Diagnostic Criteria (Reference 8)

Mania

- Duration of 1 week of an irritable, expansive, or elevated mood with at least three of the following symptoms (four if mood is irritable)
  - Distractibility (poor attention and concentration)
  - Excessive involvement in pleasurable activities (increased sexual activity, spending sprees, increased recreational drug use)
  - Inflated self-esteem
  - Racing thoughts
  - Increased goal-directed activity or agitation
  - Decreased need for sleep
  - Increase in talking (rapid, pressured speech)
- Impairment in everyday functioning or need for hospital admission
- Manic episode not caused by medications or medical conditions

Hypomania

- Duration of 4 days of an irritable, expansive, or elevated mood with at least three of the following symptoms (four if mood is irritable)
  - Distractibility (poor attention and concentration)
  - Excessive involvement in pleasurable activities (increased sexual activity, spending sprees, increased recreational drug use)
  - Inflated self-esteem
  - Racing thoughts
  - Increased goal-directed activity or agitation
  - Decreased need for sleep
  - Increase in talking (rapid, pressured speech)
- Hypomanic episode not caused by medications or medical conditions

Pediatric patients with bipolar disorder are at a high risk of suicide attempts and completion of suicide, substance abuse, and nonadherence to medication (Reference 13). Many (65.3%) patients with PBD do not "outgrow" their illness and continue to have symptoms into adulthood. In fact, patients with a diagnosis of PBD tend to have worse symptoms during adulthood and are more difficult to treat to remission (Reference 14). Patients with PBD also are at a high risk of relapse of their illness. Even when adherent to medications, patients are placed at a higher risk of relapse into mania or depression because of differences in hormonal regulation, self-medication through recreational drug use, and the kindling phenomenon (Reference 5).

Treatment

Treatment Goals

The treatment goals in PBD are to treat the current mood episode, prevent future mood episodes, minimize adverse effects, treat co-occurring conditions, and maintain or return to normal the patient's psychosocial function and quality of life. Individualized treatment is paramount, with both nonpharmacologic and pharmacologic treatments used to achieve euthymia. Although patient education is important, in PBD, parent or guardian education is equally important.

Treatment Algorithm

Treatment guidelines published by the American Academy of Child and Adolescent Psychiatry (References 5, 15, 16) exist to help clinicians determine appropriate treatment options. In addition, bipolar disorder treatment guidelines for adults are published by the American Psychiatric Association (Reference 9). Pharmacologic treatment is divided into acute treatment and maintenance treatment. Acute treatment medications are helpful in reducing symptoms of acute mania or depression. Maintenance treatment medications are helpful in preventing future mood episodes. As described below, some medications are used for both acute and maintenance treatment in PBD. In the treatment of PBD, combination medication treatment is the rule rather than the exception, but unwarranted polypharmacy should be avoided by using the least number of medications at the lowest possible dose. Recognition that pediatric patients may be more sensitive to the adverse effects of medication and that combining medications would compound these adverse effects is essential. In addition, there are relatively few (compared with the adult literature) large placebo-controlled trials and even fewer long-term studies of medications in PBD. As such, although the current recommendation is for combination treatment, individualized pharmacotherapy based on tolerability, efficacy, and patient (or caregiver) preference is of utmost importance. Because of the relative lack of data for the treatment of PBD, the adult literature is often extrapolated to the pediatric population. For acute mania, antipsychotics and mood stabilizers are used, and for acute depression, antidepressants may be added to a mood stabilizer. Both antipsychotics and mood stabilizers can be used in the long-term prevention of mood episodes. During acute treatment, medications are added to a patient's medication regimen and may be discontinued once euthymia is reached. If at any point psychosis is present, an antipsychotic should be used. Patients with PBD should continue mood stabilizer treatment indefinitely (References 5, 9, 15). See Table 3 for a summary of U.S. Food and Drug Administration (FDA)-approved medications used to treat PBD and Table 4 for other treatments that may be beneficial in PBD despite lacking FDA approval.

Nonpharmacologic treatment includes lifestyle modifications and psychosocial strategies. Stress reduction can decrease mood lability and improve quality of life. Ensuring adequate sleep through appropriate sleep hygiene and minimization of caffeine before bedtime can help prevent manic episodes. Daily exercise and adequate nutrition can also help prevent mood episodes. Eating well-balanced meals with appropriate intake of essential fatty acids, amino acids, and vitamins can help prevent mood episodes. Individual and family psychotherapies (using cognitive behavioral techniques) have also proven useful in helping improve the living environment, communication skills, problem-solving skills, and overall family dynamic. Academic and occupational functioning should be addressed, with involvement from the patient's school or job, which can improve long-term outcomes. Although minimal data exist in pediatric patients, ECT (electroconvulsive therapy) may be used for severe mania or depression (Reference 5). Other community resources are available such as the National Alliance on Mental Illness (NAMI) or Mental Health America. (See additional resources at end of chapter.)

Treatment of acute mania or mixed episode associated with PBD (ages 10–17) should be initiated with lithium, divalproex, or an FDA-approved atypical antipsychotic as monotherapy. If no response is seen, switching to monotherapy with another first-line agent is appropriate. If a partial response is seen, augmentation with another first-line agent is warranted (e.g., lithium or divalproex with an atypical antipsychotic). Combination therapy may be required in many patients, but a systematic approach should be used. Use of a medication for 4–6 weeks at therapeutic blood levels is considered an adequate trial. Patients who have psychosis (hallucinations, delusions) should be initiated on an atypical

Table 3. Medications FDA Label Approved for Pediatric Bipolar Disorder (References 15, 18–21)

Generic Name	Brand Name	Indications	Formulations	Dosage and Administration	Common Adverse Effects
Atypical Antipsychotics					
Aripiprazole	Abilify, Abilify Discmelt, Abilify IM	Acute treatment of mania or mixed episodes as monotherapy in children and adolescents 10–17 years old Irritability associated with autistic disorder in children and adolescents 6–17 years old Adolescent schizophrenia in patients 13–17 years old IM injection not approved for use in children or adolescents	Oral tablet: 2, 5, 10, 15, 20, 30 mg Orally dissolvable tablet: 10, 15 mg Oral solution: 1 mg/mL Short-acting IM injection: 9.75 mg/1.3 mL	Titration schedule: 2 mg/day for 2 days, 5 mg/day for 2 days, and then 10 mg/day. Increase by 5-mg increments when needed. Target dose: 10 mg/day Maximal dose: 30 mg/day	Somnolence, nausea, extrapyramidal symptoms, fatigue, weight gain
Olanzapine	Zyprexa, Zyprexa Zydis, Zyprexa IM, Zyprexa Relprevv	Acute treatment of mania or mixed episodes as monotherapy in children and adolescents 10–17 years old Adolescent schizophrenia in patients 13–17 years old IM injections not approved for use in children or adolescents	Oral tablet: 2.5, 5, 7.5, 10, 15, 20 mg Orally dissolvable tablet: 5, 10, 15, 20 mg Short-acting IM injection: 10-mg vial Long-acting IM injection: 210, 300, 405 mg	Starting dose: 2.5–5 mg/day, titrate by 5-mg increments Target dose: 10 mg/day Maximal dose: 20 mg/day	Weight gain, increased appetite, sedation, fatigue, dry mouth, headache
Quetiapine	Seroquel, Seroquel XR	Acute treatment of mania or mixed episodes as monotherapy in children and adolescents 10–17 years old Adolescent schizophrenia in patients 13–17 years old	Oral tablet: 25, 50, 100, 200, 300, 400 mg Oral tablet, extended release: 50, 150, 200, 300, 400 mg	Titration schedule: Using immediate-release formulation. Day 1, 25 mg BID; day 2, 50 mg BID; day 3, 100 mg BID; day 4, 150 mg BID; day 5, 200 mg BID. Increase by not more than 100 mg/day thereafter. Target dose: 400–600 mg total daily dose Maximal dose: 600 mg/day	Somnolence, dizziness, increased appetite, weight gain, dry mouth, tachycardia, fatigue
Risperidone	Risperdal, Risperdal M-tab, Risperdal Consta	Acute treatment of mania or mixed episodes as monotherapy in children and adolescents 10–17 years old Irritability associated with autistic disorder in children and adolescents 5–16 years old Adolescent schizophrenia in patients 13–17 years old IM injection not approved for use in children or adolescents	Oral tablet: 0.25, 0.5, 1, 2, 3, 4 mg Orally dissolvable tablet: 0.25, 0.5, 1, 2, 3, 4 mg Oral solution: 1 mg/mL Long-acting IM injection: 12.5, 25, 37.5, 50 mg	Starting dose: 0.5 mg/day, titrating by 0.5- to 1-mg increments Target dose: 2.5 mg/day Maximal dose: 6 mg/day	Sedation, dizziness, fatigue, nausea, extrapyramidal symptoms, weight gain
Mood Stabilizers					
Lithium	Lithium carbonate, lithium citrate, Eskalith CR, Lithobid	Acute manic episode or maintenance of bipolar disorder in adolescents 12 years and older	Oral capsule, as lithium carbonate: 150-, 300-, 600-mg capsule Oral tablet, extended release as lithium carbonate: 300, 450 mg Oral syrup, as lithium citrate: 8 mEq/5 mL	Starting dose: 300 mg BID, titrating by 300-mg increments Target dose, acute mania and maintenance: 900–1,800 mg/day, based on target lithium level of 0.6–1.2 mEq/L Maximal dose: 1,800 mg/day or blood concentration of 1.2 mEq/L	Nausea, tremor, diarrhea, weight gain, sedation

BID = twice daily; CR = controlled release; IM = intramuscular; XR = extended release.

Table 4. Other Medications with Potential Uses in PBD (References 15, 26–28)

Generic Name	Brand Name	Indications	Formulations	Dosage and Administration	Common Adverse Effects
Antipsychotics					
Clozapine	Clozaril, Fazaclo	Adult-refractory schizophrenia or schizoaffective disorder	Oral tablet: 25, 50, 100, 200 mg Orally dissolvable tablet: 12.5, 25, 100, 150, 200 mg	Starting dose: 12.5 mg at night, titrated according to package insert Target dose: 300 mg/day Maximal dose: 900 mg/day	Sedation, weight gain, hyperlipidemia, hyperglycemia, orthostatic hypotension, agranulocytosis (rare)
Paliperidone	Invega, Invega Sustenna	Adolescent schizophrenia in patients 13–17 years old Adult bipolar mania IM injection not approved for use in children or adolescents	Oral tablet, extended release: 1.5, 3, 6, 9 mg Long-acting IM injection: 39, 78, 117, 156, 234 mg	Starting dose: 3 mg/day, titrating by 3-mg increments Target: 6 mg/day Maximal dose: 6 mg/day if < 51 kg, 12 mg/day if > 15 kg	Sedation, dizziness, fatigue, nausea, extrapyramidal symptoms, weight gain
Ziprasidone	Geodon, Geodon IM	Adult bipolar mania IM injection not approved for use in children or adolescents	Oral capsule: 20, 40, 60, 80 mg Short-acting IM injection: 20 mg/mL	Starting dose: 20–40 mg BID, titrating by 20-mg increments Target dose: 40–60 mg BID Maximal dose: 80 mg BID	Sedation, headache, QT prolongation, weight gain, prolactin elevation
Anticonvulsants					
Carbamazepine	Tegretol, Tegretol XR, Carbatrol, Equetro	Adult manic or mixed episode	Oral tablet: 200, 400 mg Oral chewable tablet: 100 mg Oral suspension: 100 mg/5 mL Oral tablet, extended release: 100, 200, 400 mg Oral capsule, extended release: 100, 200, 300 mg	Starting dose: 100–200 mg BID, titrated by 100 mg every week Target dose: Titrate to desired effect. Maximal dose: 1000 mg/day	Drowsiness, dizziness, nausea, weight gain, hyponatremia
Divalproex sodium, valproic acid	Depakote, Depakote ER, Depakene, Stavzor	Adult bipolar mania or mixed episodes, maintenance of bipolar disorder in adults	Oral tablet, divalproex sodium: 125, 250, 500 mg Oral tablet, divalproex sodium, extended release: 250, 500 mg Oral sprinkle capsule, divalproex sodium: 125 mg Oral capsule, valproic acid: 250 mg Oral capsule, delayed release: 125, 250, 500 mg Oral syrup, valproate sodium: 250 mg/5 mL	Starting dose: 10–15 mg/kg/day, increasing by 5–10 mg/kg/week as needed Target dose: titrated to clinical response Maximal dose: 60 mg/kg/day	Nausea, diarrhea, tremor, sedation, weight gain
Lamotrigine	Lamictal, Lamictal XR	Prevention of mood episodes in adult patients with bipolar disorder	Oral tablet: 25, 100, 150, 200 mg Orally dissolvable tablet: 25, 50, 100, 200 mg Oral tablet, chewable: 2, 5, 25 mg Oral tablet, extended release: 25, 50, 100, 200 mg	Starting dose, monotherapy titration: 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, 100 mg/day for 1 week; then 200 mg/day Starting dose, with divalproex: 25 mg every other day (or 12.5 mg/day) for 2 weeks, 25 mg/day for 2 weeks, 50 mg/day for 1 week; then 100 mg/day Starting dose, with carbamazepine or other enzyme-inducing agents: 50 mg/day for 2 weeks, 100 mg/day for 2 weeks, 200 mg/day for 1 week; then 400 mg/day Target and maximal dose, monotherapy: 200 mg/day Target and maximal dose, with divalproex: 100 mg/day Target and maximal dose with carbamazepine or other enzyme-inducing agents: 400 mg	Headache, drowsiness, nausea, rash, dizziness
Oxcarbazepine	Trileptal	Adult manic or mixed episode	Oral tablet: 150, 300, 600 mg Oral suspension: 300 mg/5 mL	Starting dose: 150 mg BID, titrate by 150-mg increments every week Target dose: Titrate to desired effect. Maximal dose: 60 mg/kg/day	Drowsiness, dizziness, nausea, fatigue, tremor, hyponatremia

BID = twice daily; IM = intramuscular(ly); PBD = pediatric bipolar disorder; XR/ER= extended release..

antipsychotic (References 5, 15, 16). In general, tolerability seems to be better with atypical antipsychotics despite metabolic adverse effects such as weight gain, dyslipidemia, and glucose intolerance (Reference 17).

Limited data exist regarding maintenance therapy and prevention of symptom relapse for PBD. In general, if a patient had acute remission with a specific treatment modality, extended therapy with this treatment seems most likely to sustain remission. After 12–24 months of sustained remission, discontinuation of medications can be considered using a slow taper. Patients with a significant history of suicidality, aggressive behavior, or psychotic symptoms should be taken off medications with great caution. As mentioned previously, many patients require lifelong pharmacotherapy (References 5, 15, 16).

Medications for PBD

Antipsychotics

Aripiprazole, olanzapine, quetiapine, and risperidone are all FDA approved as monotherapy to treat acute manic or mixed episodes in children and adolescents aged 10–17 years (References 17–20). Based on extrapolation from adult data, aripiprazole and olanzapine have FDA approval for maintenance treatment as well (References 17, 18). Ziprasidone does not have a current approval for PBD, even in light of several positive open-label trials. The lack of approval may be because the drug manufacturer did not follow generally accepted practices and protocol when conducting the initial placebo-controlled studies (References 22–25). Although paliperidone, the active metabolite of risperidone, has no approval for PBD, it is approved for schizophrenia in patients 12–17 years old. Moreover, it shows a tolerability profile similar to its parent compound in adolescent patients (References 21, 26). Also approved for adolescent schizophrenia (ages 13–17 years) are aripiprazole, quetiapine, risperidone, and olanzapine (References 18–21). Clozapine has significant adverse effects that require frequent monitoring, and it is not FDA approved for PBD or adolescent schizophrenia but may be useful in the treatment of refractory patients who have a firm diagnosis of PBD (Reference 5). In general, lower doses of atypical antipsychotics are used in pediatric patients than in adult patients, and dose titration is more conservative. Asenapine, iloperidone, and lurasidone are newer atypical antipsychotics that currently have no indications in pediatric patients, and no literature is available to guide clinicians in their use. Long-acting injectable formulations are available for risperidone, paliperidone, and olanzapine. Although the long-acting formulations are not approved for use in pediatric patients, they may be appropriate for a small subset of patients with adherence difficulties. First-generation or typical antipsychotics have been useful for the treatment of mania, but they are not recommended because of their significant adverse effects, such as their greater propensity to cause tardive dyskinesia and extrapyramidal symptoms.

The mechanism of action of atypical antipsychotics in the treatment of PBD is not fully understood, but it is likely that dopamine (DA_2) and serotonin ($5\text{-}HT_{2A}$) receptor antagonism contribute to their efficacy in the acute treatment of mania or mixed states. This antagonism results in decreased DA_2 transmission in the mesolimbic pathway and increased DA_2 transmission in the mesocortical pathway. Atypical antipsychotics in general are well absorbed when administered orally; they are also highly lipophilic and highly bound to plasma proteins. In addition, they have long half-lives, which allow once-daily administration, except for quetiapine and ziprasidone, which are dosed twice daily. Most atypical antipsychotics are metabolized in the liver by the cytochrome P450 (CYP) pathways through CYP2D6 (risperidone major pathway, aripiprazole minor pathway), CYP3A4 (aripiprazole major pathway, quetiapine major pathway, olanzapine minor pathway, clozapine minor pathway, ziprasidone minor pathway), or CYP1A2 (clozapine and olanzapine major pathway). Only ziprasidone has no major pathway through the CYP system because it is primarily metabolized by aldehyde oxidase. Paliperidone is primarily excreted unchanged through the urine. Atypical antipsychotics rarely affect the metabolism of other medications through the CYP system. Other medications are more likely to affect the blood concentrations of the atypical antipsychotics through induction (decreased concentrations that may lead to decreased efficacy) or inhibition (increased concentrations that may lead to increased adverse effects) of the CYP system. When combined with lithium or valproate, as is often done in the treatment of mania associated with PBD, these medications do not affect the metabolism of the antipsychotics, but additive adverse effects may be seen (References 5, 15, 18–21).

Major adverse effects for each atypical antipsychotic are listed in Table 3 and Table 4. Although the atypical antipsychotics have similar adverse effects overall (sedation and weight gain), certain medications may be more likely to cause specific adverse effects. For example, risperidone and paliperidone are more likely to cause increases in prolactin (leading to gynecomastia, amenorrhea, and sexual dysfunction) and extrapyramidal symptoms. Olanzapine is more likely to cause increased weight, increased appetite, hyperglycemia, and hyperlipidemia and is recommended only after other medications have been tried. Olanzapine also has a warning for inducing ketoacidosis or hyperosmolar coma. Quetiapine is more likely to cause dizziness or sedation, and aripiprazole is more likely to cause nausea

and restlessness. Ziprasidone may also cause prolactin elevation as well as QT-interval prolongation. A baseline electrocardiogram (ECG) is recommended for pediatric patients before initiating treatment with ziprasidone. Clozapine causes significant weight gain, hyperlipidemia, hyperglycemia, sedation, and orthostatic hypotension. In addition, patients receiving clozapine need to be monitored for agranulocytosis weekly for the first 6 months, every other week for the next 6 months, and then once a month. Although rare, all atypical antipsychotics confer some risk of tardive dyskinesia and neuroleptic malignant syndrome, and the long-term risks of these adverse effects have not been fully examined in pediatric patients (References 18–21, 26–28).

Mood Stabilizers

Carbamazepine

Although data are limited with carbamazepine in PBD, some data exist regarding its use in adult patients. Carbamazepine has a tricyclic antidepressant-like structure and, as a result, has many adverse effects and is poorly tolerated overall. Carbamazepine also causes many drug interactions (e.g., with oral contraceptives) because it is a CYP3A4 inducer. In addition, it induces its own metabolism, and frequent dosage adjustments may be needed. As such, it is recommended only for patients whose other options in the management of their PBD have failed (Reference 15). Therapeutic levels of carbamazepine are 6–10 mcg/mL for the treatment of bipolar disorder. See the Seizure Disorders chapter for more information on carbamazepine.

Divalproex Sodium

Divalproex sodium has been studied in PBD with generally positive results, but it has no FDA approval for PBD (References 29, 30). Divalproex is recommended for acute mania and maintenance therapy because of its efficacy in adults. Divalproex also seems to be effective in the treatment of mixed states or rapid cycling patients because of its antikindling effect. Valproic acid, the non–enteric-coated dosage form, may also be used, but it may cause more adverse effects than divalproex. The mechanism of action of divalproex in PBD is unclear, but it may be related to its modulating effect on sodium and calcium channels and its enhancing action on GABA. More information on the mechanism of action of divalproex and its pharmacokinetics and drug interactions is available in the Seizure Disorders chapter.

Adverse effects commonly seen in pediatric patients can be found by exploring the pediatric epilepsy data and include sedation, nausea, dizziness, tremor, and weight gain. Less common adverse effects include alopecia, thrombocytopenia, and polycystic ovarian syndrome. Divalproex also has black box warnings for hepatotoxicity, pancreatitis, and increased suicide risk. Hepatotoxicity risk decreases considerably in older groups of children (older than 2 years), but divalproex should be discontinued if significant hepatic dysfunction is detected. Further information on adverse effects is available in the Seizure Disorders chapter.

Divalproex has a narrow therapeutic window, but monitoring of levels is not mandatory, unlike with lithium, because controversy exists regarding what the appropriate levels should be. In general, the therapeutic range for PBD is thought to be 50–125 mcg/mL (References 5, 15). Dosing is based on weight and is shown in Table 4.

Lamotrigine

Lamotrigine has FDA approval in the adult population to delay the time to mood episodes in patients with bipolar disorder. Data for using lamotrigine in PBD are sparse, but positive (Reference 31). Lamotrigine is not used for the treatment of acute episodes of depression or mania, but it can be useful in long-term mood stabilization. Lamotrigine has a specific dosing titration to help prevent severe cutaneous reactions from occurring (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) (see Table 4). This reaction is more common in pediatric patients younger than 16 years, and an extended titration schedule has been proposed to decrease the risk (Reference 32). In addition, lamotrigine titration schedules are different if the patient is receiving divalproex, carbamazepine, or other enzyme-inducing agents. For more information on lamotrigine, see the Seizure Disorders chapter.

Lithium

Lithium, considered the classic mood stabilizer, is FDA approved in adolescents 12 years and older for the acute and maintenance phase of PBD (References 5, 15). Much of the data regarding the efficacy and safety of lithium in pediatric patients are extrapolated from the adult literature. Favorable double-blind, placebo-controlled trials regarding the use of lithium in PBD are lacking, but open-label trials show some efficacy (References 33–38). Compared with the atypical antipsychotics, lithium in trials shows less efficacy and more adverse effects, in addition to requiring close monitoring of levels. As such, lithium is seldom used in clinical practice compared with the atypical antipsychotics.

Lithium's mechanism of action in the treatment and prevention of mania and depression is largely unknown, but lithium may have a positive effect on many of the proposed pathophysiologies in PBD such as normalizing second-messenger systems and regulating neurotransmitters and gene expression. Lithium is a monovalent cation that is rapidly absorbed when

administered orally. It has no protein binding or metabolism and is excreted unchanged through the urine. The half-life of lithium depends on renal function, but it is generally about 24 hours. Even though lithium has a half-life that would dictate once-daily dosing, it is divided two or three times/day to improve tolerability when administered as immediate-release lithium. Extended-release lithium can be dosed one or two times/day. Drug interactions occur owing to changing the elimination of lithium from the kidney. Medications such as NSAIDs (nonsteroidal anti-inflammatory drugs), thiazide diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers may cause an increase in lithium concentration because of the reduced renal excretion of lithium. When concomitant administration cannot be avoided, frequent monitoring is recommended to determine the effect of these medications on lithium concentrations. Medications such as loop diuretics and acetaminophen are less likely to cause this interaction. Other medications such as caffeine, theophylline, and acetazolamide may cause a decrease in lithium levels because of increased renal excretion.

Adverse effects of lithium are usually dose related and most common when it is first initiated and 1–2 hours postdose. Nausea, sedation, diarrhea, tremor, headache, confusion, poor concentration, polydipsia, polyuria, and weight gain are the most common adverse effects. Other, less common adverse effects include nephrogenic diabetes insipidus, flattening or inversion of the T-wave on an ECG, and leukocytosis. Lithium has negative effects on the kidney as well, with up to 20% of patients developing morphologic changes with long-term use. These changes can lead to increased serum creatinine and decreased water reabsorption in the kidney. Another organ affected by long-term lithium administration is the thyroid gland because lithium can decrease thyroid hormone synthesis and cause the formation of antibodies to the thyroid. This effect may be especially problematic for pediatric patients because thyroid hormone is essential to proper growth and development. However, long-term effects of lithium in pediatric patients have not been fully evaluated.

Lithium has a narrow therapeutic window, and blood concentrations should be monitored often. A blood concentration of 0.6–1.2 mEq/L at steady state is generally thought to be adequate for achieving therapeutic success. For acute mania, the target concentration is the upper end of this range (0.9–1.2 mEq/L); for prevention of mood episodes, the target concentration is the lower end of this range (0.6–0.9 mEq/L). A higher concentration of lithium (greater than 1.5 mEq/L) in the blood can lead to mild toxicity, as evidenced by increased or more severe adverse effects such as nausea, vomiting, ataxia, coarse tremor, or confusion. A lithium level above 2.0 mEq/L constitutes severe toxicity, and patients taking this level would have severe gastrointestinal effects, decreased coordination, seizures, slurred speech, muscle twitching, kidney failure, and cardiac arrhythmias. Administering intravenous fluids and monitoring of kidney function are important steps in managing acute lithium toxicity. Dialysis is recommended if the lithium level is above 3.0 mEq/L. To avoid toxicity, patients should have consistent noncaffeinated fluid intake, avoid activities that cause excessive sweating, and monitor their sodium intake (References 9, 15).

Oxcarbazepine

Oxcarbazepine is a structural analog of carbamazepine that was originally touted to have fewer adverse effects and drug interactions than carbamazepine. This claim is controversial, and there are more data with carbamazepine for adult bipolar disorder than with oxcarbazepine. Nevertheless, oxcarbazepine is listed on the adult guidelines for the treatment of bipolar disorder and recommended whenever carbamazepine could be used. There has been only one PBD trial, which showed no difference from placebo in the treatment of mania (Reference 39). As such, its use is not currently recommended in PBD. See the Seizure Disorders chapter for more information on oxcarbazepine.

Adjunctive Treatments

When clinicians treat patients with PBD in the depressed phase, they have little evidence to draw on in the PBD population to help make treatment decisions. Antidepressants, lamotrigine, quetiapine, olanzapine/fluoxetine combination, and lithium have been used in adults to treat bipolar depression with success, but data in pediatric patients are lacking (References 9, 15, 16). Extrapolating from the adult data, certain antidepressants such as tricyclic antidepressants (e.g., amitriptyline, imipramine) and serotonin and norepinephrine reuptake inhibitors (e.g., venlafaxine, duloxetine) seem more likely than selective serotonin reuptake inhibitors (e.g., citalopram, paroxetine) and norepinephrine and DA reuptake inhibitors (bupropion) to induce mania. Combining antidepressants with mood stabilizers in PBD is a prudent strategy to help reduce the risk of a potential switch to mania (References 5, 15). Lamotrigine and lithium have been studied in PBD in open-label trials with positive results, but more data are needed before they can be routinely recommended (References 40, 41). A study investigating the use of quetiapine in PBD showed no difference from placebo (Reference 42). For more information on antidepressants, see the Pediatric Depression chapter.

Benzodiazepines have also been used in adults as short-term treatment for acute mania or mixed episodes as a sedative-hypnotic. This strategy may not be optimal in pediatric patients because disinhibition and agitation may occur as adverse effects more often in this population than in adults. In addition, established guidelines do not mention the use of benzodiazepines in PBD, and data are lacking in the pediatric population on this topic (References 5, 15).

Other therapies that have been studied include omega-3 fatty acids and flaxseed oil. Omega-3 showed modest efficacy in an open-label trial, but flax oil failed to separate from placebo in a randomized controlled trial (References 43, 44).

Monitoring Parameters

When monitoring patients for efficacy, the Young Mania Rating Scale (YMRS) has been used successfully in pediatric patients. The YMRS can be useful in tracking specific symptoms and responses to medications over time (Reference 45). Close follow-up (within 4–6 weeks) to assess efficacy, adverse effects, and adherence is recommended when the drug is initiated (Reference 15).

Metabolic monitoring for atypical antipsychotics in adult patients is described in a consensus document (Reference 46), and when using these medications in pediatric patients it seems prudent to follow the same guidelines. Baseline measurements include weight, height, blood pressure, fasting glucose and lipids, waist circumference, and personal and family medical history. Weight should be monitored monthly for the first 3 months and then every 3 months. Fasting glucose and lipids as well as blood pressure should be monitored after 3 months and then every year. Waist circumference is monitored yearly, together with a reassessment of personal and family medical history. Additional baseline laboratory assessments should include a CBC, LFTs, thyroid function tests, and a BMP, which are then monitored periodically throughout treatment. Adolescent girls who have reached menarche should also have a urine pregnancy test at baseline. A baseline ECG is recommended before ziprasidone use, and prolactin levels may be obtained as clinically warranted. When monitoring for tardive dyskinesia, administration of an AIMS (Abnormal Involuntary Movement Scale) is recommended every 6 months (References 5, 15).

Lithium levels are recommended every week for the first month, monthly for the first 3 months, and then every 3 months. A minimum of 5 days on lithium therapy should elapse before drawing levels to ensure attainment of steady state. Lithium levels are most accurate before the morning dose, 12 hours after the evening dose. As mentioned above, a lithium level of 0.6–1.2 mEq/L is considered therapeutic. Baseline safety monitoring of lithium consists of a BMP, a CBC, thyroid function tests, a measure of weight, a reading of fasting glucose and lipids, an ECG, and a pregnancy test in female adolescents of childbearing potential. These parameters should be obtained after 3 months on lithium and then, if normal, every 6–12 months (References 9, 15).

Anticonvulsant monitoring parameters are available in the Seizure Disorders chapter, but generally, LFTs, weight, fasting glucose and lipids, BMP, CBC, and a pregnancy test should be obtained at baseline and then periodically throughout treatment. Divalproex and carbamazepine levels reach steady state after 3 and 4 days, respectively, but are not required to be drawn as frequently as lithium levels. Although monitoring levels for divalproex and carbamazepine is prudent, the level itself should not become the therapy goal; levels should be viewed as part of the overall treatment response, with symptom resolution or prevention being the primary goal.

Special Populations

Female adolescents who have reached menarche should be counseled on the risk of birth defects from medications used to treat PBD. Lithium can cause fetal heart abnormalities (Ebstein anomaly), and divalproex and carbamazepine can cause neural tube defects. Recently, the FDA updated the package labeling for atypical antipsychotics to include more consistent risks in pregnancy (Reference 47). Adequate contraception is recommended to females who are sexually active or who may become sexually active. Furthermore, carbamazepine reduces the effectiveness of oral contraceptives, and patients should be counseled to use another method of birth control while being treated with this medication. Treatment of PBD during pregnancy should be discussed with the patient and obstetrician and is usually handled by physicians who specialize in high-risk pregnancy.

In addition, ADHD and PBD commonly occur together. Treatment of ADHD can be especially difficult in patients with PBD because stimulants may precipitate a manic episode. Stimulants should be used cautiously and only when ADHD symptoms fail to resolve with adequate bipolar disorder treatment. Atypical antipsychotics should not be used to treat ADHD symptoms in patients without bipolar disorder, but they have shown some efficacy in co-occurring ADHD and bipolar disorder (Reference 17).

Conclusions

Pediatric bipolar disorder is a serious mental illness that can be treated successfully with a combination of psychosocial interventions and medications. Although data are lacking for the acute and long-term management of

PBD, there are FDA-approved treatments. Lithium is FDA approved for maintenance treatment of PBD, and aripiprazole, olanzapine, quetiapine, and risperidone are approved for acute treatment of mania. Other treatments such as divalproex, lamotrigine, and other anticonvulsants have not been FDA approved, but they may prove useful in PBD. Careful diagnosis and appropriate treatment of PBD can result in improved outcomes and better quality of life for patients and families affected by PBD.

Additional Resources

- American Academy of Child and Adolescent Psychiatry, www.aacap.org
- Mental Health America, www.nmha.org, (800) 969-6642
- National Alliance on Mental Illness, www.nami.org, (800) 950-NAMI

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CHAPTER 30

Attention-Deficit/Hyperactivity Disorder

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Learning Objectives

1. Describe the signs and symptoms of attention-deficit/hyperactivity disorder.
2. Identify the primary mechanisms of action of stimulants and non-stimulants.
3. List common adverse events among pharmacologic agents.
4. Identify rare, life-threatening adverse events of pharmacologic agents.
5. Discuss advantages and disadvantages among pharmacologic agents.

Abbreviations in This Chapter

ADHD	Attention-deficit/hyperactivity disorder
ADHD RS-IV	ADHD Rating Scale-IV
CRS-R	Conners Rating Scales-Revised
DRDs	Dopamine receptor genes
DAT1	Dopamine transporter gene
DSM-IV-TR	Diagnostic and Statistical Manual for Mental Disorders (4th ed., text rev.)
HNMT	Histamine degradation gene
MAOIs	Monoamine oxidase inhibitors
SNAP-IV	Swanson, Nolan, and Pelham-IV questionnaire
TCAs	Tricyclic antidepressants

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the most commonly diagnosed childhood psychiatric disorders. In general, ADHD may display two types of symptoms: inattentive and hyperactive/impulsive types (see Table 1). Those with inattentive symptoms may display careless mistakes or can be easily distracted by external factors. Patients with ADHD who display symptoms of hyperactivity/impulsivity may have difficulty sitting still, may be unable to play quietly, or may blurt out answers before the teacher has finished asking the question.

Consequences of ADHD can include poor school and social functioning for the child. If left untreated, ADHD may lead to increased rates of not completing high school, unemployment, unwanted pregnancy, sexually transmitted diseases, traffic accidents, and incarceration (References 1–3). In addition, increased rates of substance abuse and diagnosis of a major psychiatric disorder (e.g., bipolar, anxiety) have been cited in adults with ADHD (Reference 4). Having a child with ADHD can also create a significant amount of stress among caregivers and teachers. Finding the best pharmacologic agent to treat and manage symptoms, together with educational and behavioral therapies, is of utmost importance for this patient population. With many agents available, it is crucial that practitioners select the optimal medication(s) that may serve to appropriately treat symptoms while minimizing adverse events.

Epidemiology

The prevalence of ADHD ranges from 3% to 20% in school-aged children, depending on the criteria and sample population used (Reference 5). However, it is estimated that the worldwide prevalence is 5%, although it appears to be almost 9% in the United States (References 6, 7). The differences in prevalence may be because of the ways in which studies classify "functional impairment" in their patients (Reference 8). Persistence into adolescence and adulthood may reach 85% and 31%, respectively (References 9, 10). The adult prevalence is estimated at 2.5% because it is believed that some patients "outgrow the disease," undergo neurobiologic maturation, or find better coping mechanisms to adapt to the environment as they grow older (Reference 11). However, caution is warranted because some believe that patients do not really "outgrow the disease," but rather, outgrow the diagnostic criteria set forth by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.) (DSM-IV) (References 12, 13).

Etiology

There appears to be a genetic predisposition to ADHD. Studies have shown the heritability of ADHD is about 77% when at least one parent has ADHD (Reference 14). Several genetic/biologic markers in ADHD have been studied including the 480-bp allele, the dopamine transporter gene (*DAT1*), and the dopamine receptor genes (*DRDs*) (Reference 15). The gene with the strongest association in ADHD appears to be the 7-repeat allele of the dopamine receptor D4 gene (*DRD4*)

Table 1. DSM-IV-TR Diagnostic Criteria for ADHD (Reference 21)

"Persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequently displayed and is more severe than is typically observed in individuals at comparable level of development." Individual must meet criteria for either (1) or (2):

1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
b) often has difficulty sustaining attention in tasks or play activity
c) often does not seem to listen when spoken to directly
d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
e) often has difficulty organizing tasks and activities
f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
h) is often easily distracted by extraneous stimuli
i) is often forgetful in daily activities

2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

a) often fidgets with hands or feet or squirms in seat
b) often leaves seat in classroom or in other situations in which remaining seated is expected
c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
d) often has difficulty playing or engaging in leisure activities quietly
e) is often "on the go" or often acts as if "driven by a motor"
f) often talks excessively

Impulsivity

a) often blurts out answers before questions have been completed
b) often has difficulty awaiting turn
c) often interrupts or intrudes on others (e.g., butts into conversations or games)

A. Some hyperactive-impulsive or inattentive symptoms must have been present before age 7 years.
B. Some impairment from the symptoms is present in at least two settings (e.g., at school [or work] and at home).
C. There must be clear evidence of interference with developmentally appropriate social, academic, or occupational functioning.
D. The disturbance does not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorders and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Note: A new, highly anticipated version, the DSM-V, is expected in 2013 with possible changes in ADHD diagnosis, which include changing the "age of onset" from 7 to 12 and reclassifying the subtypes of symptoms (i.e., inattention, hyperactivity, impulsivity). ADHD = Attention-deficit/hyperactivity disorder; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed., text rev.). Reprinted with permission from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision, (Copyright 2000). American Psychiatric Association.

(Reference 16). However, this has been questioned because the association was still small, and there is yet to be an actual gene associated with ADHD (Reference 17). In addition, studies suggest that a genetic predisposition in patients predicts their treatment response (Reference 18). For example, those with a 9-repeat allele show poor response to methylphenidate treatment (Reference 18). Recent data also report that copy number variants, which are submicroscopic chromosomal abnormalities, may be implicated in ADHD (e.g., excess of 16p13.11 duplications) (Reference 19).

Environmental triggers associated with ADHD are countless and may include smoking during maternal pregnancy, lead exposure, low birth weight, and severe social deprivation during early infancy (Reference 8). Certain foods (e.g., chocolate, eggs, peanuts) and artificial colors or dyes (e.g., yellow #5, red #3, blue #1) may also exacerbate hyperactive symptoms of ADHD. Of interest, it has been hypothesized that a histamine degradation gene *(HNMT)* is responsible for hyperactive responses to food dyes (Reference 20).

Diagnosis

The main types of symptoms associated with ADHD include inattention and hyperactivity/impulsivity. The DSM-IV criteria for diagnosis further describe the common symptoms of ADHD, which are listed in Table 1. The literature on ADHD may classify patients as predominantly inattentive, predominantly hyperactive/impulsive, or combined type, in which the patient displays a combination of symptoms. Common features of inattention include difficulty organizing activities, sustaining attention, and following through on instructions as well as being easily distracted by extraneous stimuli (Reference 21). For example, young Debbie sits in the classroom but does not listen attentively in class or successfully complete her assignments, and she often misplaces her pencils and books (i.e., predominantly inattentive type). Hallmark features of hyperactivity include often fidgeting with hands or feet, leaving the seat in classroom, and having difficulty engaging in leisure activities quietly. Impulsive symptoms may also be present, which include having difficulty awaiting one's turn and interrupting others. For example, young Johnny disrupts the classroom by running around at inappropriate times, answering out of turn, and constantly talking with surrounding classmates (i.e., predominantly hyperactive/impulsive type). In addition, young Jamie has difficulty following directions when spoken directly to (e.g., does not follow orders), avoids completing assignments, talks excessively with classmates, and squirms excessively in the chair (i.e., combined type). Females tend to display inattentive symptoms, whereas males tend to display hyperactive symptoms (Reference 22). As a result, by comparing the examples above (i.e., Debbie, Johnny), teachers and parents may be more prone to refer males (3:1) for diagnosis because hyperactivity will more likely disrupt the classroom or home setting. However, for a proper diagnosis, these behaviors must be present before age 7, occur in two or more settings (e.g., home, classroom), and cause significant impairment in the child's social and academic development.

Rating Scales

Several scales are used to measure ADHD symptoms (Reference 23). These scales primarily identify specific symptoms that can assist in diagnosing and identifying the subtypes of ADHD. The most commonly known scales include the Conners Rating Scales-Revised (CRS-R); IOWA Conners scale; Swanson, Nolan, and Pelham-IV questionnaire (SNAP-IV); and ADHD Rating Scale-IV (ADHD RS-IV). Newer scales, including the Vanderbilt ADHD Rating Scales (VARS) and the ADHD Symptoms Rating Scale (ADHD-SRS), have been developed to capture symptoms/manifestation of conduct disorders, anxiety, or depression (e.g., VARS) and to increase the subtlety of the ways in which ADHD affects social functioning (e.g., ADHD-SRS) (References 23, 24). The time required to complete the scales varies. Some scales such as the CRS-R, SNAP-IV, and ADHD-SRS may take 20–30 minutes to complete, whereas others such as the IOWA Conners, ADHD RS-IV, and VARS may take only 5–15 minutes to complete (Reference 23). All six scales can be completed by parents or teachers. Some scales (e.g., IOWA Conners, SNAP-IV, ADHD RS-IV, ADHD-SRS) may be divided into two or three subscales, whereas other scales (e.g., CRS-R, VARS) may have four to seven subscales (Reference 23). Of note, most of these scales were derived from criteria in the DSM-IV, therefore predominantly targeting male symptoms (Reference 23). Thus, caution is needed when using these scales to evaluate females.

Pathophysiology

The pathophysiology of ADHD is complex, showing overall decreased cerebral volume. Specific regions of the brain that consistently show a reduction in size in ADHD include the caudate nucleus, prefrontal cortex white matter, and cerebellar vermis (References 25, 26). Impairment of the prefrontal cortex and anterior cingulate cortex, which are responsible for controlling appropriate behaviors and inhibitions, appears to be the primary culprit in the manifestation of ADHD (References 8, 27, 28). It is theorized that a prefrontal cortex abnormality exists that causes a dysregulation of two primary neurotransmitters: dopamine and

norepinephrine. Dopamine appears to be active in the mesocortical pathways responsible for aspects of cognitive function including verbal fluency, serial learning, executive function, and sustaining attention (References 28, 29). Norepinephrine appears to be active in the prefrontal pathway responsible for mediating energy/fatigue, motivation, moderation of behavior on the basis of social cues, and sustaining of attention (Reference 29). Of note, unlike in other psychiatric illnesses (e.g., depression, schizophrenia, bipolar disorder), serotonin does not seem to play a major role in ADHD. As a result, selective serotonin reuptake inhibitors may be given to those with ADHD who also have a psychiatric comorbidity such as major depression; however, they are clinically useless in the treatment of ADHD.

Treatment

Nonpharmacologic Treatments

The best nonpharmacologic treatment available at this time appears to be behavioral therapy, usually given concomitantly with some form of educational session. Behavioral therapy attempts to eliminate or limit inappropriate behaviors by reinforcing desired behaviors. Some short-term studies have shown that behavioral therapy can improve ADHD symptoms, especially in the home environment when used with pharmacologic agents (Reference 30). However, it is not fully clear whether using behavioral therapy as adjunctive treatment will decrease medication dosage. Long-term (3-year) studies show that behavioral therapy may decrease future incidences of delinquency or substance abuse (Reference 31). Therefore, behavioral therapy may be considered monotherapy or adjunctive treatment to pharmacologic agents (Reference 32). Behavioral therapy may be used as monotherapy if symptoms are mild, ADHD diagnosis is unclear, or parents refuse pharmacologic agents (References 8, 32). However, therapy sessions can be costly, and insurance plans may only cover a limited number of sessions. In addition, there may be a lack of trained professionals (e.g., psychologists, psychiatrists) in certain parts of the country, and identifying a qualified therapist may not be possible.

Diets and certain herbal supplements to treat ADHD have been popular through the years. The Kaiser Permanente (also known as Feingold diet) or elimination diet, which works at eliminating foods containing synthetic additives (e.g., benzoate preservatives) or dyes, has been studied to evaluate its effectiveness in treating symptoms of ADHD (References 33–35). Some trials have shown a significant decrease in behaviors (e.g., hyperactivity) when elimination diets were used (Reference 33). However, the differences might not have been clinically significant and were only noted on the parents' rating scales, with no changes noted on the health care providers' ratings. It also appears the improvement in behaviors occurred in all children despite ADHD diagnosis, leading to the belief that artificial food dyes and preservatives should be limited in all children (References 33, 34). In addition, elimination diets cause a widely varying response among patients, which may be caused by genetic variability (e.g., *HNMT*) (References 20, 33). Therefore, future pharmacogenomic testing may identify those with a higher sensitivity (e.g., greater hyperactive response) to certain foods or additives. Elimination diets may prove highly effective in a small selection of patients; however, these treatment options should not be used to replace prescription therapy (e.g., stimulants).

Most diets rich in omega-3 fatty acids have shown no greater efficacy than placebo (Reference 36). However, recent data suggest that a combination of essential fatty acids including eicosapentaenoic acid, docosahexaenoic acid, and γ-linolenic acid provides some benefits for inattention (Reference 35). The benefits of these fatty acids, although small, may not be seen for 3 months. Homeopathy has also been studied, and despite showing some improvements, data appear to be inconsistent and subject to interpretation. As a result, these interventions offer minor relief of symptoms in studies with weak methodologies and prone to bias (e.g., parents vs. physician rating scales) (References 8, 36). Therefore, at this time, vitamin-rich diets and homeopathy are not generally recommended, and further studies are needed.

Vitamins and herbals such as ginkgo biloba and ginseng have been used to improve attention, whereas zinc, valerian root, and lemon balm have been used for symptoms of hyperactivity/impulsivity (References 35, 37–40). Data supporting other agents (e.g., St. John's wort, L-carnitine, Pycnogenol) are weak (References 35, 37). Despite some benefits in open-label studies (e.g., zinc), adverse events are inadequately measured in most of these studies, and most are subject to bias. In addition, they provide few benefits, and the ingredients are not standardized or monitored by the U.S. Food and Drug Administration (FDA), therefore possibly leading to undesirable consequences (References 8, 40). In conclusion, the use of herbal supplementations should be avoided in the treatment of ADHD.

Pharmacologic Treatments

Treatment Guidelines

The Texas Children's Medication Algorithm project revised the ADHD guidelines in 2006 (Reference 32). However, as new data are disseminated, guidelines for ADHD are revised and updated. Table 2 is a guideline based on new data and differs slightly from other guidelines (Reference 32). Of note, any of these stages can be skipped, if necessary. If partial response occurs at a

particular stage, some agents may be added adjunctively, as previously discussed. In addition, remember that behavioral therapy may be added during any stage. Primary comorbidities of other psychiatric conditions (e.g., Tourette syndrome, psychosis, major depression) may require different pharmacologic treatment guidelines.

Stimulants

Stimulants are controlled substances (C-II) that have been used extensively for many years. Stimulants are separated into two classes: amphetamines and methylphenidate products. Stimulants are considered first-line agents for the treatment of ADHD, with a response rate of 65% to 75% in double-blind placebo-controlled studies or as high as 90% in other trials (References 41, 42). When both types of stimulants are tried, efficacy rates increase to 85% to 90% (References 41, 42). Despite some minor differences in the actual mechanism of action, stimulants are theorized to work by increasing norepinephrine and dopamine concentrations through reuptake inhibition. Methylphenidate is believed to occupy dopamine transporters, resulting in dopamine reuptake inhibition, which causes D_1-receptor activation (References 43, 44). In addition, recent data indicate that methylphenidate occupies norepinephrine transporters, thereby increasing norepinephrine and dopamine (norepinephrine transporters actually have more affinity toward dopamine) in the prefrontal cortex (Reference 45). Amphetamines increase the release of dopamine through an exchange mechanism (sodium-dependent transport protein) and by binding to dopamine transporter proteins on the exterior of the cell membrane, causing dopamine reuptake inhibition (Reference 44). In addition, amphetamines presynaptically block the reuptake of norepinephrine, thereby increasing the concentration in the synaptic cleft (Reference 44).

At this time, no clinical preference exists regarding the stimulant that should be initially selected. Stimulants exist in a variety of formulations, and generics are readily available (see Table 3). Therefore, the selection of an agent will depend on these characteristics. Onset of action with stimulants can range from 15 to 120 minutes, and duration ranges from 3 to 12 hours, depending on the formulation (References 8, 46). When selecting an agent, the formulation should be carefully considered. Children weighing less than 16 kg should be routinely initiated on short-acting stimulants (References 41, 46). Overall, if symptoms are targeted that occur mostly in school, a short-acting agent is preferred. If problems persist after school (e.g., difficulty studying, completing homework), another dose of the short-acting agent can be used. However, this may cause medication burden on teachers or caregivers, especially if the child has difficulty taking the medication in the first place (References 8, 24). Therefore, it is usually better to change to an intermediate-acting formulation. If ADHD symptoms occur at all times, then a long-acting

Table 2. Pharmacologic Treatment Guideline

Stage 1	Stimulants: Methylphenidate or amphetamine products Note: Although some may prefer to start with methylphenidate because of its possibly lower adverse effects, others may choose to start with amphetamines because of more favorable kinetics.
Stage 2	Stimulant class not used in stage 1
Stage 3	Atomoxetine
Stage 4	Bupropion or guanfacine Note: Bupropion may be preferred if a secondary comorbidity of depression exists. Guanfacine may be preferred if tics are an issue. Practitioners may prefer the extended-release formulation of guanfacine, but costs may hinder its use.
Stage 5	Agent not used in stage 4
Stage 6	TCA or Clonidine Note: A TCA may be preferred if a secondary comorbidity of depression exists. Clonidine may be preferred if tics are an issue. Practitioners may prefer an extended-release formulation of clonidine, but costs may hinder its use.
Stage 7	Agent not used in stage 6

TCA = tricyclic antidepressant.

Table 3. Pediatric Pharmacologic Treatment of ADHD—Stimulants (References 8, 41, 46)

	Brand Name (generic)	Dosage Forms (mg)	Duration of Action (hr)	Initial Dose (mg); Maximal Daily Dose (mg)	Daily Dosing Range (mg)
Amphetamine Products	Adderall (amphetamine/ dextroamphetamine)	Tablets (5, 7.5, 10, 12.5, 15, 20, 30)	Intermediate acting (4–6)	3–5 yr: 2.5 QAM ≥ 6 yr: 5 QD or 2.5 BID Maximal dose: 40	10–40
	Adderall XR (amphetamine/ dextroamphetamine)	Capsules (5, 10, 15, 20, 25, 30)	Long acting (8–12)	6–17 yr: 10 QAM Maximal dose 6–12 yr: 30	5–30
	Dexedrine Spansule (dextroamphetamine)	Spansules (5, 10, 15)	Intermediate acting (5–8)	≥ 6 yr: 5 QAM-BID Maximal dose: 40	5–40
	Dextrostat/Dexedrine (dextroamphetamine)	Tablets (5, 10)	Short acting (3–5)	3–5 yr: 2.5 QAM ≥ 6 yr: 5 QAM-BID Maximal dose: 40	0.1–0.5 mg/kg/ dose
	Vyvanse (lisdexamfetamine)	Capsules (20, 30, 40, 50, 60, 70)	Long acting (10–12)	≥ 6 yr: 30 QAM Maximal dose: 70	30–70
Methylphenidate Products	Ritalin (methylphenidate)	Tablets (5, 10, 20)	Short acting (3–5)	≥ 6 yr: 5 BID Maximal dose: 2 mg/kg or 60	10–60
	Ritalin SR (methylphenidate SR)	Tablets (20)	Intermediate acting (3–8)	≥ 6 yr: 20 QAM Maximal dose: 60	20–60
	Ritalin LA (methylphenidate LA)	Capsules (10, 20, 30, 40)	Long acting (8–12)	≥ 6 yr: 20 QAM Maximal dose: 60	20–60
	Methylin (methylphenidate)	Solution 5 mg/5 mL, 10-mg/5-mL Tablets (5, 10, 20) Chewable tablets (2.5, 5, 10)	Short acting (3–5)	≥ 6 yr: Tablet: 5 mg BID before breakfast and lunch Solution: 0.3 mg/kg/dose BID Chewable tablet: 2.5 BID Maximal dose: 2 mg/kg/day or 60	Tablet: 10–60 Solution: 10–60 Chewable tablet: 0.5–1 mg/kg/day
	Methylin ER (methylphenidate ER)	Tablets (10, 20)	Intermediate acting (3–8)	≥ 6 yr: 10 QAM Maximal dose: 60	10–60
	Metadate ER (methylphenidate ER)	Tablets (20)	Intermediate acting (3–8)	≥ 6 yr: 20 QAM Maximal dose: 60	20–60
	Metadate CD (methylphenidate CD)	Capsules (10, 20, 30, 40, 50, 60) Bimodal drug release 30% IR, 70% ER	Long acting (8–12)	≥ 6 yr: 20 QAM Maximal dose: 60	10–60
	Concerta (methylphenidate OROS)	Tablets (18, 27, 36, 54) Bimodal drug release (OROS) 22% IR 78% ER	Long acting (8–12)	≥ 6 yr: Not currently taking methylphenidate: Concerta 18 QAM Currently taking methylphenidate 5 BID-TID or 20 ER QAM: Concerta 18 QAM Currently taking methylphenidate 10 mg BID-TID or 40 ER QAM: Concerta 36 QAM Currently taking 15 BID-TID or 60 ER QD: Concerta 54 QAM Currently taking 20 BID-TID: Concerta 72 QAM	6–12 yr: 18–54 13–17 yr: 18–72
	Daytrana (methylphenidate)	Transdermal patch 10 mg/9 hr, 15 mg/9 hr, 20 mg/9 hr, 30 mg/9 hr	Long acting (12) wear for 9 hr only	6–17 yr: 10-mg patch daily—wear for up to 9 hr Maximal dose: 30 mg/9 hr	10–30 patch/9 hr
	Focalin (dexmethylphenidate)	Tablets (2.5, 5, 10)	Short acting (3–5)	2.5 BID Maximal dose: 20	5–20
	Focalin XR (dexmethylphenidate)	Capsules (5, 10, 15, 20, 30) Bimodal drug release 50% IR, 50% ER	Long acting (8–12)	5 QAM Maximal dose: 30	10–30

BID = twice daily; CD= controlled delivery of the modified release formulation; CR = controlled release; hr = hour(s); ER/XR = extended release; IR = immediate release; LA = long acting; OROS =osmotic release oral system; QAM = every morning; QD = every day; SR = sustained release; TID = three times/day; yr = year(s).

formulation is preferred (Reference 24). In addition, if a child cannot tolerate short-acting formulations, he or she may be changed to an intermediate- or long-acting formulation because either of these would provide lower peak concentrations and/or possibly decrease the number or severity of adverse effects (e.g., tics, nausea). However, the intermediate- and long-acting formulations may take about 1 hour longer than the short-acting agents before efficacy is seen. Therefore, short-acting agents can sometimes be combined with long-acting formulations to provide extra coverage during a specific period (e.g., school hours) (Reference 46). Conversely, if a child is taking a long-acting formulation and he or she is having difficulty sleeping or eating properly, he or she may be changed to an intermediate- or short-acting agent dosed in the morning; therefore, the medication will be mostly eliminated by evening. This should allow the child to eat a large-calorie meal for dinner and sleep better. Stimulants are usually initiated at low doses and titrated to appropriate efficacy for 2–4 weeks or until unwanted adverse effects occur (Reference 24). After selecting a stimulant, careful dose evaluation over time must be noted as the child grows older. If discontinuing stimulants, tapering is usually not required.

Drug interactions among stimulants exist. Because stimulants increase the amount of monoamines (e.g., dopamine, norepinephrine) into the synaptic cleft, they should not be administered concomitantly or within 2 weeks of discontinuing a monoamine oxidase inhibitor (MAOI) (Reference 47). Amphetamines are primarily metabolized by cytochrome P450 (CYP) 2D6 (References 8, 47). Therefore, caution is warranted if strong CYP2D6 inhibitors are used (e.g., desipramine, paroxetine, fluoxetine) because they may increase amphetamine concentrations and increase the potential for cardiac complications (References 8, 47). Conversely, methylphenidate is metabolized by de-esterification and does not undergo oxidative metabolism. However, the combination of methylphenidate and tricyclic antidepressants (TCAs) may lead to an increase in TCA concentrations through an unknown mechanism (Reference 47). The literature mainly focuses on increased imipramine concentrations with methylphenidate; however, no interactions between desipramine and methylphenidate have been reported (References 47, 48).

Adverse Events

Common adverse effects among stimulants include headaches, dizziness, nausea, reduced appetite, weight loss (about 3 kg during the first year; about 1 kg during the second year), stomach pain/cramps, irritability, and insomnia. When addressing appetite suppression/weight loss, it is recommended to give a high-fat meal in the evening when stimulant effects are lower. Giving a high-fat meal (e.g., during the day) with a stimulant may also be a way to decrease stomachache or nausea; however, certain formulations may have altered kinetics when given with food (Reference 49). For example, amphetamine/dextroamphetamine (e.g., Adderall) may show more than a 50% reduction in plasma concentrations when given with a high-calorie meal (Reference 49). Overall, increases in blood pressure (about 2–7 mm Hg) and heart rate (about 5 beats/minute) are also noted with stimulants in the literature (References 50–53).

Rare but severe adverse events include increased blood pressure and tics. These adverse events may be treated by lowering/splitting the dose or switching agents. Black box warnings for stimulants include sudden death caused by heart-related problems and new/worsening psychiatric manifestations (References 54, 55). Sudden death has been reported in around 35 pediatric patients (Reference 41). Unknown structural defects are believed to have accounted for these deaths. The risk of sudden death is estimated at 0.2 and 0.5 per 100,000 children for methylphenidate and amphetamine products, respectively (Reference 56). The risk of sudden death in the general untreated population is 0.6–6 (Reference 57). There is debate on whether baseline electrocardiograms should be required. However, at this time, the American Academy of Pediatrics recommends that practitioners obtain the patient's history and physical examination before initiating therapy (Reference 55). Psychiatric complications such as mania, hallucinations, aggression, anxiety, and dysphoria are rare but potentially dangerous. The FDA recommends that children who display any psychiatric complications be discontinued on or tapered off the stimulant as quickly as possible.

Growth suppression is highly noted among stimulant use. Among 29 studies, estimated growth suppression of 1 cm/year during the first 3 years occurs with stimulants (Reference 58). It is suggested that amphetamines cause a slightly greater effect on growth suppression than methylphenidate (Reference 59). A drug holiday (e.g., during the summer) may be recommended, but an assessment of risk versus benefit for the child should be done (Reference 8). If a drug holiday is initiated, do not reinitiate treatment at the beginning of the school year. Instead, start a few weeks before to allow the child and parent to readjust and make any dosing changes, if necessary. Remember, the child may grow/gain weight during the drug holiday and therefore may need a dose adjustment.

Amphetamine Products

Amphetamine products include amphetamines, dextroamphetamines, and lisdexamfetamine, which is a prodrug to dextroamphetamine. Short-acting amphetamine products include Dextrostat and Dexedrine. Intermediate-acting products include Adderall and

Dexedrine Spansule. Long-acting formulations include Adderall XR and Vyvanse (References 8, 46). Advantages over methylphenidate products may include more predictable kinetics. In addition, formulations such as Dexedrine Spansule, Adderall XR, or Vyvanse can be opened if the child cannot swallow tablets (References 8, 46). However, the contents should not be poured over hot food. Vyvanse, a prodrug of dextroamphetamine, may have less abusive potential than other amphetamines because of its longer onset of action (Reference 60). General disadvantages of amphetamines over methylphenidate products include possible greater abuse potential, slightly higher rate of causing/worsening tics, and greater growth suppression.

Methylphenidate Products

Methylphenidate products include methylphenidate and dexmethylphenidate. Short-acting methylphenidate products include Ritalin, Methylin, and Focalin. Intermediate-acting products include Ritalin SR, Methylphenidate SR, Methylin ER, and Metadate ER (References 8, 46). Long-acting formulations include Concerta, Metadate CD, Ritalin LA, Focalin XR, and Daytrana. Daytrana (patch) should be rotated daily at different sites. Advantages over amphetamines may include less likelihood to suppress appetite, worsen tics, and cause insomnia. Formulations such as Ritalin LA, Metadate CD, and Focalin XR may also be opened (Reference 8). General disadvantages of methylphenidate products may include more erratic kinetics, especially with short-acting agents, and greater differences reported between brand and generic formulations (Reference 46). In addition, caution with gastrointestinal obstruction may be needed with Concerta, and parents should be counseled that the capsule will appear intact in the stool (Reference 46).

Non-stimulants

Atomoxetine

Atomoxetine is a non-stimulant, non-controlled agent that is FDA approved for the treatment of ADHD (Reference 61). It acts by selectively inhibiting the presynaptic reuptake of norepinephrine. Clinical trials have shown that atomoxetine is between 63% and 80% effective and can treat all symptoms of ADHD (References 61, 62). It also appears to be around 55% effective in patients whose stimulant therapy has failed (Reference 63).

Atomoxetine is usually initiated at 0.5 mg/kg/day and titrated to reach a target daily dose of 1.2 mg/kg (see Table 4). Titration should occur over a minimum of 3 days, with most waiting at least 1–2 weeks before titrating. Dosing can be increased to a maximum of 1.8 mg/kg/day. Efficacy may not be seen for 2–4 weeks, and some data suggest 6 weeks is needed for optimal benefits (References 41, 61, 62). Some patients may respond to the lower doses, whereas others may benefit from higher doses. Therefore, patience is warranted when this agent is titrated. Atomoxetine is considered a second-line agent after stimulants have failed. It can be used as monotherapy or in combination with other agents (Reference 32). It may also be preferred in those who have high abuse potential, those who are afraid of using stimulants, and those with the possible comorbidity of anxiety (Reference 41).

Atomoxetine can be administered once or twice daily. When considering once-daily dosing, there is debate regarding whether to administer in the morning or at bedtime (Reference 42). Single bedtime dosing may be used for those who are having difficulties with adverse effects (especially sedation); however, drug concentrations may be low by the morning, thus limiting its efficacy. Morning doses will provide higher concentrations in the morning, thereby increasing efficacy, but they may predispose patients to higher adverse effects. Therefore, most providers choose twice-daily dosing because of more stable plasma concentrations and possibly better tolerability. Atomoxetine can also be taken with or without food and can be discontinued without tapering.

Atomoxetine is highly metabolized by the CYP2D6 pathway (Reference 61). The half-life of atomoxetine is about 5 hours, but in poor metabolizers, it can be as long as 20 hours. As a result, plasma concentrations can increase 5- to 10-fold in poor metabolizers, and dose adjustment is warranted (Reference 61). In addition, dose adjustment or slower titration may be needed with the coadministration of other potent CYP2D6 inhibitors such as paroxetine and fluoxetine (Reference 61). Of note, atomoxetine is highly protein bound (98%); therefore, interactions with other highly protein-bound drugs are possible, although data are lacking in this area. Finally, atomoxetine should not be administered with MAOIs, and a minimum of 2 weeks is needed before initiating atomoxetine after MAOI discontinuation or vice versa.

Common adverse events of atomoxetine include abdominal pain (18%), decreased appetite (16%), vomiting (12%), somnolence (10%), irritability (7%), fatigue (7%), dizziness (5%), and dyspepsia (5%) (Reference 61). Somnolence, fatigue, and dizziness are more common with atomoxetine than with a stimulant. An increased heart rate of about 8 beats/minute and mild increased blood pressure (around 2–3 mm Hg) are also noted with atomoxetine (Reference 61). However, studies show the adverse effects are usually mild and well tolerated, with discontinuation rates caused by adverse events between 4% and 10% (Reference 61). Growth suppression is about 0.4 cm during a 2-year period, which is smaller than that with stimulants (Reference 64). Black box warnings for atomoxetine include hepatic failure (two cases occurred: one adult, one

Table 4. Pediatric Pharmacologic Treatment of ADHD—Non-stimulants (References 8, 41, 46, 61, 69–71, 74)

	Brand Name (generic)	Dosage Forms (mg)	Initial Dose (mg); Maximal Daily Dose (mg)	Daily Dosing Range (mg)	Special Notes
NE Selective Agonist	Strattera (atomoxetine)	Capsules 10, 18, 24, 40, 60, 80, 100	≥ 6 yr ≤ 70 kg: 0.5 mg/kg/day; maximum: 1.4 mg/kg/day > 70 kg: 40 QD; maximal dose: 100	≤ 70 kg: 1.2 mg/kg/day > 70 kg: 80	FDA approved, norepinephrine reuptake inhibitor. Carry less weight/ growth concerns vs. stimulants.
DA/NE Antidepressant	Wellbutrin (bupropion)	Tablets 75, 150 Extended release 150, 300 Sustained release 100, 150, 200	≥ 6 yr: 1.4–6 mg/kg/day; maximal dose: 300	50–300	Dopamine and norepinephrine reuptake inhibitor. Can worsen tics, irritability.
α_2-Adrenergic Agonists	Intuniv (guanfacine)	Tablets, extended release 1, 2, 3, 4	≥ 6 yr: 1 AM; maximal dose: 4	1–4	FDA approval for Intuniv/Kapvay. Adjust Intuniv in increments of no more than 1 mg/week. Intuniv and Kapvay are long-acting formulations. Sedation may be helpful for sleep. Agents helpful for tic comorbidities. In children, wearing patch for 5 days = 7 duration of action.
	Tenex (guanfacine)	Tablets, short acting 1, 2	≥ 6 yr: 0.5–1 HS; maximal dose: 27–40 kg: 2 41–45 kg: 3 > 45 kg: 4	1–3	
	Kapvay (clonidine)	Tablets, extended release 0.1	0.1 HS; maximal dose: 0.4	0.1–0.4	
	Catapres (clonidine)	Tablets 0.1, 0.2, 0.3 Patch (TTS) 0.1/24 hr, 0.2/24 hr, 0.3/24 hr	≥ 6 yr: < 45 kg: 0.05 HS > 45 kg: 0.1 HS; maximal dose: 27–40 kg: 0.2 41–45 kg: 0.3 > 45 kg: 0.4	0.1–0.4	
Tricyclic Antidepressants	Pamelor (nortriptyline)	Capsules 10, 25, 50, 75	≥ 6 yr: 0.5 mg/kg/day; maximal dose: 100	50–100	Give in divided doses with higher dose at bedtime. Sedation may be helpful for sleep. Sudden death reported with desipramine (consider TCAs last line).
	Tofranil (imipramine)	Capsules 75, 100, 125, 150 Tablets 10, 25, 50	≥ 6 yr: 1 mg/kg/day; maximal dose: 200	75–200	
	Norpramin (desipramine)	Tablets 10, 25, 50, 75, 100, 150	6–12 yr: 1 mg/kg/day; > 12 yr: 25–50 maximal dose: 150	25–150	

DA = dopamine; HS = at bedtime; NE = norepinephrine; QD = every day; TCA = tricyclic antidepressant.

teenager, both fully recovered), new-onset suicidal ideations (0.4%), and sudden death caused by heart complications (risk 0.5/100,000) (References 41, 62). Abuse potential is also much lower than with stimulants.

Atomoxetine is only available in capsule form, and at this time, no generic formulation exists. Although the manufacturer of atomoxetine (Eli Lilly) states the capsule cannot be opened, the data on file suggest the contents may be dissolved in 60 mL of juice (i.e., Tropicana 100% apple juice, Welch's 100% grape juice, fruit punch–flavored Gatorade). After waiting 5 minutes for dissolution to occur, it may be stable at room temperature for 6 hours. However, atomoxetine has a very bitter taste that, despite attempts to mask, may cause an increase in gastrointestinal complications. In addition, atomoxetine is an ocular irritant, so extreme caution is warranted when handling.

Bupropion

Bupropion is a norepinephrine and dopamine reuptake inhibitor used off-label for the treatment of ADHD. The usual starting dose for ADHD treatment is about 1.5 mg/kg/day, with titration over 7 days to a target dose of 3 mg/kg/day; however, it may be titrated to 6 mg/kg/day not to exceed 300 mg/day (see Table 4) (References 8, 65). Efficacy rates range from 60% to 70%, mostly treating symptoms of hyperactivity. Bupropion can be given once or twice daily; however, data suggest twice-daily dosing is more tolerable and efficacious (Reference 66). Most common adverse events reported include nausea, irritability, and insomnia (References 8, 67). In addition, rash has been reported in a few cases (Reference 67). There are some reports of decreased appetite, but they appear to be less severe compared with stimulants. However, tremors (e.g., tics) may also manifest, and seizures may occur in doses exceeding 400–450 mg/day (Reference 46). Efficacy is not seen for a minimum of 2 weeks at the therapeutic doses, and it may take up to 6 weeks for optimal results to be seen. Bupropion is contraindicated in those with seizure or eating disorders (e.g., bulimia, anorexia), and it carries a black box warning for new-onset suicidality (Reference 46). Bupropion may have utility in those who have a comorbidity of depression or in patients who are high-risk substance abusers (Reference 32). It can be used adjunctively or as monotherapy after first- and second-line agents have failed. Currently, it may be preferred over TCAs because of its safer cardiovascular profile and better tolerability compared with TCAs.

Bupropion is available as immediate release, and various extended-release formulations and generic alternatives exist. Bupropion, similar to other antidepressants, should not be administered with MAOIs, and a minimum of 2 weeks is needed before initiating bupropion after MAOI discontinuation or vice versa. Tapering of bupropion is recommended if it is being discontinued.

Tricyclic Antidepressants

Antidepressants known as TCAs have been studied for ADHD. Even though TCAs are serotonin and norepinephrine reuptake inhibitors, the primary neurotransmitter involved in the treatment of ADHD with these agents is norepinephrine (Reference 44). Recall that serotonin does not play a role in ADHD, which is why selective serotonin reuptake inhibitors are ineffective. Imipramine, nortriptyline, and desipramine are the most commonly used TCAs. However, desipramine has been associated with cardiac-related sudden death in pediatric patients and is generally avoided (Reference 41). The usual starting dose for treatment of ADHD is 0.5–1 mg/kg/day with titration to 2–3 mg/kg/day up to a maximum of 2–4 mg/kg/day (see Table 4) (Reference 41). Therapeutic range is usually between 50 and 150 mg/day, and doses are usually divided into two or three daily doses. Efficacy rates among TCAs are about 70%, mostly targeting symptoms of hyperactivity. Benefits are not seen for at least 2 weeks, and maximal efficacy may not be reached for at least 4 weeks.

The most common adverse effects are sedation, dizziness, constipation, and weight gain (References 41, 44). Caution with heart complications (e.g., increased heart rate) and cardiac toxicity is warranted. As a result, an electrocardiogram should be done at baseline and with each dose increase (Reference 41). Tricyclic antidepressants also carry a black box warning for new-onset suicidality, similar to all antidepressants. Because of the adverse event profile of TCAs, they are usually reserved as third-line agents. They may be used adjunctively and may have utility in patients with comorbidity of tic disorders, depression, or enuresis. Tricyclic antidepressants are available as capsules, tablets, and solution. These agents should not be administered with MAOIs, and a minimum of 2 weeks is needed before initiating a TCA after MAOI discontinuation or vice versa. If discontinuing, tapering of these agents is recommended.

α2-Adrenergic Agonists

Guanfacine and clonidine are the two most commonly used α_2-agonists used to treat ADHD (see Table 4). Most data suggest that these agents primarily block norepinephrine presynaptically; however, some studies also support the postsynaptic blockade of norepinephrine (Reference 44). These agents may also increase blood flow to the prefrontal cortex (Reference 68).

Guanfacine and clonidine have been used for many years with documented efficacy. Extended-release tablet formulations have recently become available in an attempt to offer greater adherence, less kinetic fluctuations, and better tolerability (References 69, 70). Even though the extended-release formulations are supposed to offer greater tolerability than the immediate-release formulations, adequate studies are lacking to compare the formulations of these agents (Reference 71). Currently, both guanfacine (i.e., Intuniv) and clonidine extended release (i.e., Kapvay) have FDA indications as monotherapy or adjunctive therapy for ADHD. Of note, deaths have been reported with the coadministration of clonidine and immediate-release stimulants; this coadministration should therefore be avoided (Reference 46). Optimal efficacy may not be reached for at least 2–4 weeks with these agents (Reference 69). Despite data showing efficacy in all symptoms of ADHD, there appears to be more efficacy toward hyperactivity/impulsivity. These agents may be especially useful in those who have a comorbidity of tics and aggressive/oppositional disorders. In addition, these medications should be tapered by weekly increments if they are to be discontinued (Reference 69).

Guanfacine

Guanfacine is metabolized and eliminated equally (50/50) by hepatic and renal elimination (References 71, 72). It is primarily metabolized by CYP3A4. Immediate-release formulations may be initiated at 0.5 mg/day or twice daily and may be increased to 1–4 mg/day in divided doses (References 8, 69). The extended-release formulation is initiated at 1 mg/day and titrated weekly by 1 mg/day to a target of 2–4 mg/day (Reference 71). Even though the extended-release formulation of guanfacine should not be crushed, the short-acting formulation may be crushed. High-fat meals should be avoided with the extended-release formulation because of increased exposure. Efficacy rates range from 60% to 80%, and adverse effects include somnolence (about 40%), headache (about 25%), fatigue (about 15%), upper abdominal pain (about 10%), hypotension (about 8%), irritability (6%), nausea (about 6%), and dizziness (about 6%) (References 69, 71). Serious less-frequent adverse events include syncope (2%) and convulsions (0.4%). Most of the adverse events appear to be dose related (References 69, 70, 73). Guanfacine may be theoretically preferred to clonidine because of its longer half-life and its higher selectivity at the α_{2a}-receptor, thereby leading to less dizziness and sedation (Reference 8). However, no comparison studies exist at this time.

Clonidine

Clonidine is 40% to 50% hepatically metabolized and 50% to 60% renally eliminated. Immediate-release formulations may be initiated at 0.05 mg/day and titrated weekly by 0.05 mg/day to a target of 0.1–0.4 mg/day in divided doses two to four times/day. The extended-release formulation is initiated at 0.1 mg and titrated weekly by 0.1 mg to a target of 0.2–0.4 mg/day (Reference 74). Twice-daily dosing is still needed for extended-release clonidine, especially with doses greater than 0.1 mg, with the higher dose given in the evening (Reference 75). Efficacy rates range from 60% to 70%; adverse events are similar to those of guanfacine and appear to be dose related. The short-acting formulation of clonidine may be crushed; however, the extended-release formulation should not be crushed or chewed. Food has no effect on any formulation. Moreover, be aware that the weekly patch is effective for 5 days in children compared with 7 days in adolescents.

Miscellaneous Agents

Other agents for the treatment of ADHD have been used, including modafinil, mood stabilizers, and antipsychotics. Modafinil (commonly used for narcolepsy) at 300 mg (dose daily or in divided doses) has shown some benefits over placebo, but the quality of the data is regarded as low (Reference 36). In addition, adverse effects such as severe rashes and psychiatric complications make this agent a last-line alternative. Those with a comorbidity of bipolar or severe aggressive behaviors may be treated with divalproex or carbamazepine (Reference 8). Low-dose antipsychotics may also be used; of these, most of the literature is focused on haloperidol, risperidone, and quetiapine. These agents should be used with caution and reserved as last-line agents.

Conclusions

Behavioral therapy used with educational sessions appears to be the best nonpharmacologic treatment. Elimination diets may be useful in a few patients; however, such diets should not be used to replace pharmacotherapy. Studies with vitamins and herbal products have shown some possible benefits; nevertheless, most trials are subject to bias, and adverse events have not been adequately addressed or evaluated. As a result, the primary treatment of ADHD focuses on pharmacotherapy with prescription medications. There are many pharmacologic agents and formulations (e.g., short, long acting) to choose from in the treatment of ADHD. Stimulants (i.e., amphetamines, methylphenidate) are considered first line and have a much faster onset and higher efficacy rates than non-stimulants. Atomoxetine is a non-controlled agent that may be used as an alternative in those whose response to stimulants is partial or has failed or in those who refuse to use a controlled substance. Literature suggests antidepressants (e.g., bupropion, TCAs) can be considered treatment options, especially in those with depressive symptoms. However, bupropion is preferred because of its tolerable and safer adverse effects. An increase in data indicates that α_2-agonists, especially with long-acting formulations, have shown good efficacy and may be considered alternative agents in ADHD. Among α_2-agonists, it appears guanfacine is the preferred agent because of its higher selectivity to receptors and the availability of a daily formulation. Miscellaneous agents (e.g., mood stabilizers, antipsychotics) may be used if the comorbidity of other psychiatric illnesses is present. Despite the agent chosen, careful monitoring is recommended for any changes in efficacy or for the development of rare but potentially serious adverse events.

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CHAPTER 31

Eating Disorders in Children and Adolescents

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Learning Objectives

1. Outline the clinical presentation of anorexia nervosa, bulimia nervosa, and binge eating disorder.
2. Describe medical complications associated with eating disorders.
3. Outline diagnostic criteria for eating disorders.
4. Discuss pharmacologic and nonpharmacologic treatments for eating disorders.
5. Understand the limitations of current diagnostic criteria and eating disorder research.

Abbreviations in This Chapter

AN	Anorexia nervosa
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
CBT	Cognitive behavioral therapy
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision
DSM-V	*Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition
EDNOS	Eating disorder not otherwise specified
FBT	Family-based therapy
GI	Gastrointestinal
IPT	Interpersonal psychotherapy
SSRI	Selective serotonin reuptake inhibitor

Introduction

Eating disorders in children and adolescents are complex disease states associated with high rates of morbidity and mortality. The number of children and adolescents with eating disorders has increased steadily during the past 60 years (References 1–3), whereas the age of onset has steadily declined (References 1, 4, 5). Hospitalizations for children younger than 12 years with diagnoses of eating disorders have increased by 119% since the late 1990s (Reference 5). The typical patient with an eating disorder has changed as well. At one time, eating disorders were considered an illness seen primarily in wealthy young white women; now, these disorders are increasingly seen in minorities (References 6–8), in males (References 9, 10), and in countries where eating disorders were once relatively unknown (References 11, 12).

Epidemiology

Recognizing and treating eating disorders at their earliest stage is imperative to achieve positive outcomes in these disorders. According to NHANES (the National Health and Nutrition Examination Survey), the 12-month prevalence rate of eating disorders, based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR), is 0.1% (Reference 13). The prevalence of the two most common eating disorders, anorexia nervosa (AN) and bulimia nervosa (BN), was equivalent (0.1%).

A challenge to the current prevalence data is that most children and many adolescents do not meet the DSM-IV-TR criteria for eating disorders, so they are either undiagnosed or are given a diagnosis of eating disorder not otherwise specified (EDNOS). The prevalence of EDNOS is between 0.8% and 14% (Reference 14). The EDNOS is not a lesser form of the eating disorders, and it should be treated promptly and aggressively, if necessary. Interventions occurring at an earlier stage of these potentially life-threatening disease states are associated with an improved prognosis (Reference 15).

Etiology

The etiology of the various eating disorders is still unknown, but it appears certain that many factors contribute to the development of an eating disorder (Reference 16). Although debated, dieting, especially severe dieting, may lead to the onset of these disorders (References 15, 17). Other etiologic factors include genetics, biologic and psychological predispositions, and environmental, social, and cultural factors.

Social, cultural, and environmental factors regarding what an ideal weight and shape are and their relationship to what is culturally considered beautiful often influence the way females think and feel about their bodies. Dieting is not uncommon in industrialized countries; in fact, most women admit that they have attempted a diet. Although diet is considered an

entry point into the development of an eating disorder, less than 3% of all females will actually develop an eating disorder (Reference 17). In one study, severe dieters were 18 times more likely to develop an eating disorder than were non-dieters (Reference 18). In nations that are less industrialized and less exposed to Western culture, the prevalence of eating disorders is much lower (Reference 19).

Studies of twins and families with at least one member having an eating disorder suggest a genetic link in the development of eating disorders. Studies of monozygotic and dizygotic twins have shown high concordance rates, although the studies themselves have shown differing results. Some studies have shown that the greatest concordance is between monozygotic twins, whereas others have shown higher rates with dizygotic twins (References 20–23). In families having at least two members with either AN or BN, genomic studies show initial linkage regions on chromosomes 1, 3, and 4 in AN and on chromosome 10p in BN. Additional genomic studies are being conducted (Reference 24). Together with the genetic risk, it is believed that psychological factors may influence eating disorder development. Traits such as perfectionism, inflexibility, a drive to be thin, a need for control, and interpersonal distrust have all been proposed as factors that affect the onset of eating disorders (Reference 25). Traits that are common in eating disorders are also associated with several psychiatric conditions. The incidence of depression and other mood disorders is 50% to 80% in patients with both AN and BN. There is a 30% to 65% incidence of anxiety, especially obsessive compulsive disorder, and a 20% to 80% incidence of personality disorders, especially borderline personality disorder, in patients with AN and BN (Reference 22).

The neurotransmitters serotonin, dopamine, and norepinephrine increasingly appear to play a role in the etiology of eating disorders. Serotonin is known to play a role in appetite, mood, and stress response. Serotonin antagonists increase food cravings and intake, which leads to weight gain. The serotonin metabolite 5-hydroxyindoleacetic acid is often found to be low in those who are underweight, but the level corrects itself once normal weight is achieved (References 26–28). In patients who have recovered from AN, norepinephrine is lower than the level that exists in control populations (Reference 29). Dopamine may also be related to eating disorder etiology. Common symptoms that may be linked to dopamine dysregulation include distortion of body image and obsessive compulsive behaviors (References 30, 31).

Leptin, a hormone produced in adipose tissue, is related to weight regulation and energy balance. In addition, leptin appears to play a significant role in mediating eating disorders. Patients with AN tend to have a decrease in leptin levels because of low levels of circulating fat. These low leptin levels signal low energy levels to the brain. Patients who have recovered from eating disorders continue to have lower levels of serum leptin based on their body mass index (BMI). It is possible that both leptin and norepinephrine serve as trait markers for patients with eating disorders, but more research needs to be completed to confirm this association (References 32, 33).

Medical Complications

Eating disorders have the highest mortality rates of all the psychiatric disorders at a rate of 4% (References 34, 35). Medical complications associated with these disorders are especially lethal in children and adolescents. Suicidality is a risk factor associated with eating disorder–related mood changes and dissatisfaction with body image (Reference 35).

According to the Agency for Healthcare Research and Quality, the hospitalization rate because of malnutrition for children younger than 12 rose by 119% between 1999 and 2006 (Reference 5). There are frequently long-term consequences associated with eating disorders, even once resolution of disordered eating behaviors has occurred. These consequences include osteopenia, structural changes to the gray and white matter of the brain, growth retardation, and pubertal delay (Reference 36). With time, the body is unable to compensate for long-term nutritional deficits, causing metabolic rate declines and inhibition of temperature regulation. Ultimately, almost all organ systems are affected by the effect of malnutrition on the body (References 37–39).

Malnutrition and starvation lead to dysfunction of the endocrine system including hyperactivity of the hypothalamo-pituitary axis. These changes have effects on thyroid function and the reproductive system, leading to hypothyroidism, hypogonadism, hypercortisolism, and amenorrhea. In addition, endocrine dysfunction can lead to growth retardation and a delay in the onset of puberty in children and adolescents. These effects on the hypothalamo-pituitary axis as well as the inability of growth hormone to bind to insulinlike growth factor-1 may all be part of the mechanism of growth retardation (References 36–39). Unfortunately, the effects on growth, especially on short stature, may be a permanent manifestation of malnutrition (Reference 40).

Weight loss causes a decrease in the volume of the gray and white matter of the brain and cerebrospinal space (Reference 41). Cognitive dysfunction often occurs in patients with eating disorders secondary to hypercortisolism and hypogonadism (Reference 42). Magnetic resonance imaging has shown changes in

brain activity. From neuroimaging, it appears that volumetric decreases in gray matter caused by malnutrition may be permanent, whereas white matter may improve with refeeding (References 42, 43).

Hypogonadism, amenorrhea, and nutritional deficiencies lead to low bone marrow density. This is a significant problem for children and adolescents because this period of growth is important for bone mineralization. It is unclear whether refeeding will reverse these changes on bone mineral density (References 44, 45).

Eating disorders cause significant damage to the gastrointestinal (GI) tract. The effects on the GI tract include delays in gastric emptying, gastroesophageal reflux, and GI bleeding. Constipation is a common occurrence caused by nutritional deficits. Enlargement of the salivary glands is associated with hyperemesis (Reference 46). Self-induced vomiting can cause a callus on the dorsum of the hand called Russell's sign. Repeated forced emesis can also cause a separation of the mucosal membrane between the esophagus and stomach that may lead to extensive bleeding called a Mallory-Weiss tear. Stomach acid from hyperemesis may also cause dental erosion.

Dehydration from purging behaviors leads to imbalances in fluid and electrolyte status. In addition, hyperemesis may lead to a hypochloremic metabolic alkalosis because of the loss of hydrochloric acid. The body's attempt to conserve fluid in the face of dehydration can lead to hypokalemia-causing cardiac arrhythmias. Hypomagnesemia from malnutrition can lead to sudden cardiac death. Likewise, malnutrition and/or laxative abuse can induce hypoproteinemia, which can lead to significant edema and, potentially, congestive heart failure. Dehydration caused by laxative abuse may induce a hyperchloremic metabolic acidosis. Dilutional hyponatremia may be seen in patients who attempt to improve their weight before visiting their health care provider (References 38–40, 46, 47).

Finally, malnutrition can lead to stomatitis; dry, cracked, scaly skin; and hair and nail changes. The development of lanugo, a fine soft hair that covers the body, and yellow skin coloring are not uncommon in patients with eating disorders (References 38–40).

Patient Assessment

Eating disorders can have an adverse effect on every organ system, so a thorough medical and psychosocial evaluation should be completed for patients with these disorders. In addition to a complete physical examination, laboratory measures should be taken, including an electrolyte panel, liver function tests, a complete blood cell count, thyroid function tests, and glucose, calcium, and magnesium concentrations. In patients with amenorrhea, a serum pregnancy test, serum estradiol, serum prolactin, and follicle-stimulating hormone should be measured. In addition, in female patients with amenorrhea, a bone scan should be completed to check for osteopenia. An electrocardiogram should be considered for those with electrolyte abnormalities or cardiovascular symptoms. Neuroimaging of the brain should be considered for those with severe malnutrition (Reference 48).

It is important for the clinician to recognize that laboratory results may be normal in patients with eating disorders and that normal laboratory results should not exclude either the diagnosis or the treatment of an eating disorder. Patients should be assessed on the basis of their symptoms because medical instability can be overlooked by clinicians who base their decisions on laboratory results alone. Clinicians also need to be aware that patients with AN and BN tend to be ambivalent about treatment, and it is common for them to hide their illness. Thus, denial by the patient does not exclude the possibility of an eating disorder. With time, these disorders can become egosyntonic, meaning that the behaviors provide positive reinforcement for the patient, and changing the behavior is more frightening than living with it (References 48, 49).

Psychosocial evaluations should include an assessment of how the patient views food, nutrition, and their current body image. Social factors such as their relationships with significant others, including parents, siblings, friends, and other support systems, should be assessed. Because eating disorders often co-occur with other psychiatric conditions such as mood, anxiety, and personality disorders, these psychiatric disorders should be assessed as well. A complete medical history, including use of illicit drugs and over-the-counter medications such as laxatives, stimulants, and diuretics, should be obtained. It is important to discuss with the patient if there is any history of sexual, physical, or emotional abuse because these can play a role in the development of eating disorders. It is not uncommon for patients with an eating disorder to complete a suicide, so evaluating the patient's risk is an important part of an initial patient evaluation and ongoing clinical care (Reference 49).

Standardized Rating Scales

A variety of assessment measures exist for evaluating eating disorders. Some of these measures include semi-structured interviews, self-reporting, symptom checklists, and clinical rating scales. The most commonly used assessment measures are the Eating Disorders Examination, the Yale Brown Cornell Eating Disorder Scale, the Eating Attitudes Test, the Eating Disorder Inventory, and the Eating Disorder Questionnaire. Any member of the eating disorder treatment team, including psychiatrists, psychologists, pharmacists, dietitians, nurses, or social workers, can be trained to provide interviews for the various scales.

The Eating Disorders Examination is a semi-structured interview with four subscales (restraint, eating concern, shape concern, and weight concern). The advantage of this examination is that it allows the clinician to develop a diagnosis, which is selective for certain eating behaviors such as binge eating. A disadvantage to using this scale is that it should be administered by a trained interviewer, and it can take up to 1 hour to complete (Reference 50).

The Yale Brown Cornell Eating Disorder Scale is also a semi-structured interview with a 65-item checklist and questions that cover ritualistic and obsessive behaviors sometimes seen in patients with eating disorders. This scale takes 15 minutes to complete (Reference 51).

The Eating Attitudes Test is a self-report measure that includes a full-scale 50-item test and a brief 26-item measure that evaluates for global eating disorder symptoms. The Eating Attitudes Test is sensitive to treatment effects (Reference 52). The Eating Attitudes Test for children is called the Children's Eating Attitudes Test. It contains 26 items, and scores greater than 20 are considered associated with developing an eating disorder (Reference 53).

Another standardized self-report measure, the Eating Disorder Inventory, evaluates patient attitudes and their behaviors around food, body image, and weight. The Eating Disorder Inventory also measures patient attitudes concerning perfection, effectiveness, trust, and maturity. The Eating Disorder Inventory is sensitive to treatment effects (Reference 54). The Eating Disorders Questionnaire is also a self-report measure. It covers eating disorder symptoms and demographic information (Reference 55).

Self-reports are simple and take a minimal amount of time to complete. They are inexpensive and objective, avoiding rater bias. The primary disadvantage of these scales is that they may be less accurate than the semi-structured interviews.

Anorexia Nervosa

Anorexia nervosa is one of the most serious psychiatric disorders that can occur in children and adolescents. The presentation of anorexia has occurred in children as young as 7 years old (Reference 56). Patients with anorexia are often perfectionists and high achievers who, under stress-induced situations, use caloric restriction as a means of controlling situations in which they otherwise have no control (Reference 57). Initially, this weight loss may be reinforced by positive comments from friends and family admiring it. Continued weight loss is associated with obsessions and compulsions that provide secondary reinforcement, which then becomes a vicious cycle (Reference 57).

Epidemiology

The incidence of AN in adolescent females between age 15 and 19 years is 0.48% to 0.7% (Reference 58). Early-onset AN, the occurrence of anorexia in prepubertal children or children younger than 14 years, occurs in 5% of all cases (References 56–60). Although we tend to think of AN as being a disease of females, in the prepubertal population, boys and girls have an equal incidence of this disorder, with some thought that at very young ages, boys may actually show a greater incidence of anorexia (Reference 61). At least one-third of the individuals with AN develop a chronic disorder that is marked by relapse and recurrent hospitalizations (Reference 62).

Clinical Presentation

The core feature of AN involves a refusal to maintain body weight of at least 85% of the optimal weight for age and height. Body dysmorphism, a distortion in one's body image, is a primary reason for the refusal to maintain weight. Once weight is lost, the patient has a fear of gaining weight or becoming fat. In children and adolescents, this level of malnutrition prevents normal growth patterns, including a delay in sexual maturation, which leads to amenorrhea in females. Patients with AN may either restrict their intake of food or binge and purge. Patients with AN can meet the diagnostic criteria for BN (such as having binge/purge behaviors). However, they will retain the diagnosis of AN as long as they remain at least 15% below their ideal body weight and meet the DSM-IV-TR criteria for AN. In addition to restricting caloric intake and developing extensive food rituals, patients with AN often participate in excessive exercise to inhibit weight gain (Reference 63).

Diagnostic Criteria

The diagnostic criteria from the DSM-IV-TR are listed in Table 1.

Risk Factors

One risk factor for developing AN is having a family history of an eating disorder. Family studies have shown that there is a 3% lifetime risk of developing anorexia in first-degree relatives (References 21, 64). Parental eating behavior and weight may also play a role. A recent study showed that families who sat down to dinner most days in the week were less likely to develop anorexia than families who did not (Reference 65). Personality traits such as having a "type A personality" or being a perfectionist may be a risk factor. Mood symptoms in patients and their first-degree relatives may also put patients at an increased risk of developing anorexia. Many patients with anorexia were mildly overweight before developing the disorder (Reference 65).

Course and Prognosis

Anorexia nervosa has the highest mortality rate of all the eating disorders. The mortality risk is estimated to be 10% within 10 years of an AN diagnosis and is primarily caused by starvation or suicide (References 35, 66).

Anorexia nervosa has significant comorbidity with other psychiatric disorders. In patients who restrict food intake, obsessional behaviors such as repetitive and/or intrusive thoughts, perfectionism, and inflexibility are common. In patients with AN who purge, suicidality and self-harm are common. Mood disorders and anxiety disorders are common to both anorexia subtypes (Reference 67).

If the disorder is treated in the early stages of development, especially in prepubertal adolescents in whom weight restoration is achieved, outcomes appear to be good. In patients with anorexia who continue to refuse to maintain minimum weights, there is a tendency to initiate binging and purging behaviors that may evolve into a diagnosis of BN (References 67, 68).

Treatment of AN

The initial treatment goal in AN is to restore the patient's nutritional status and treat the medical complications. The degree of malnutrition dictates how to best medically manage the patient. In the initial approach, it is imperative to determine the degree of electrolyte and nutrient loss before the patient's nutritional status can be appropriately restored. Restoration of electrolytes (e.g., potassium, sodium, and magnesium) and of calcium, folic acid, zinc, and iron must occur early in the process of refeeding (Reference 69). Once patients are less than 75% of their ideal body weight, are medically unstable, or have a heart rate less than 50 beats/minute, they should be hospitalized (Reference 69).

Because these patients have been in starvation mode, it is important to improve the energy deficits early by slowly titrating energy calories. Restoring deficits in children is of greater concern than in adolescents and adults. Children may have lower energy or fat stores, and they may dehydrate more rapidly. Body mass index is unreliable in children and young adolescents who have not finished growing. Growth may be stunted, and assessing appropriate weight gain in the still-growing youth is difficult (References 69, 70).

The initial goal for inpatients is to gain 0.3–0.4 lb per day, and the initial goal for outpatients is to gain 1–2 lb per week. Recommendations on how to achieve this weight gain vary, but it is considered reasonable to start refeeding with between 1000 and 1600 calories daily and to titrate upward slowly as tolerated. Most patients will begin to achieve an adequate level of weight gain with an intake of between 2200 and 2500 calories daily. As energy requirements are replaced and the level of physical activity resumes, the metabolic rate will normalize, and the rate of weight gain will decline (References 69, 70).

The clinician must take care not to cause refeeding syndrome. Refeeding syndrome occurs when an individual is fed normal quantities of food too quickly after a long period of starvation. When a patient is in starvation mode, insulin secretion declines because of a reduced intake of carbohydrates. Protein stores are broken down first, followed by fat stores to provide energy to the individual. During this level of starvation,

Table 1. DSM-IV-TR Criteria for Anorexia Nervosa (Reference 63)

A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected)
B. Intense fear of gaining weight or becoming fat, even though underweight
C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight
D. In postmenarchal women, amenorrhea (i.e., the absence of at least three consecutive menstrual cycles). (A woman is considered to have amenorrhea if her periods occur only after hormone therapy [e.g., estrogen administration].)
Specify type:
Restricting Type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)
Binge Eating/Purging Type: During the current episode of anorexia nervosa, the person has regularly engaged in binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)

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intracellular electrolytes are reduced. Intracellular phosphate levels are at particular risk of depletion, although extracellular phosphate, which is typically measured in laboratory results, appears normal. Once normal feeding resumes, the body shifts from breaking down fat to breaking down carbohydrates once again. The cycle is reversed, insulin is secreted, and phosphates are shifted intercellularly. This leads to a profound extracellular hypophosphatemia. The serum phosphate concentration, usually less than 0.5 mmol/L, causes refeeding syndrome. Refeeding syndrome is characterized by hypotension, arrhythmias, seizures, cardiac failure, respiratory failure, rhabdomyolysis, coma, and sudden death. Refeeding syndrome can occur with not only oral feeding, but also parenteral or enteral feedings (Reference 71).

Once patients have stopped losing weight, their weight has started to trend upward to at least 75% of their ideal body weight, and their laboratory results have normalized, they can go to a supportive home, where they can continue to work with a dietitian and therapist on a regular basis. If a supportive environment is not available, patients may go to a day treatment program, where they can be monitored for progress toward their weight gain goals.

Nonpharmacologic Treatment

Once the patient is stabilized medically, the next stage in treatment is to focus on developing new dietary habits as well as changing cognitive response to eating, weight, and the underlying psychopathology that led to the eating disorder.

At one time, environmental factors in families were thought to be the cause of eating disorders, but this theory has been dismissed. In the past decade, research suggests that family therapy is the most beneficial treatment for AN. In family therapy, called family-based treatment or family-based therapy (FBT), parents initially take responsibility for the child's or adolescent's eating behaviors. It is the family's job to ensure that the patient is eating adequately and avoiding eating disorder behavior. Once patients have regained at least 85% of their normal weight, children or adolescents slowly become responsible for their own eating. In the last treatment phase, the patient and family work toward resuming what would be a normal developmental stage for the child or adolescent (Reference 72).

At least five controlled trials of FBT show promise for this treatment, especially in children or adolescents with a short illness (References 72–77). Family-based therapy typically takes 6–12 months to complete, and the outcomes have been durable at the 5-year follow-up (References 73–78).

Family-based therapy is typically advised for intact, supportive families. In families where the affected child has been abused, or in the most nutritionally and medically compromised patients, FBT would not be the treatment of choice (Reference 72). In these patients, cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT) should be considered.

Cognitive behavioral therapy teaches the patient strategies to cope with feelings and events that initially led to the eating disorder. In addition, CBT improves self-esteem and helps the patient correct body image distortions (Reference 79). Interpersonal psychotherapy typically focuses on interpersonal problems that may play a role in eating disorder behaviors.

Pharmacologic Treatment

There are no randomized controlled trials of any pharmacologic agent for the treatment of AN in children or adolescents alone. Some trials have been completed in adolescents and adults, but most of these studies were either too short or used medication doses that today would be considered insufficient for the treatment of an eating disorder. In addition, studies that have been published typically do not have the statistical power required to make evidence-based decisions.

If medications are used in AN, they should be considered for the co-occurring psychiatric conditions frequently seen with AN, rather than for treatment of the eating disorder alone.

Pharmacologic treatments for AN have included antidepressants, antipsychotics, cyproheptadine, hormones, and zinc. Most randomized controlled trials completed in adults have been with the antidepressants. The tricyclic antidepressants clomipramine and amitriptyline have been studied for the treatment of AN. Clomipramine caused increased appetite, which did not carry over to weight gain in patients (Reference 80). Amitriptyline has been studied in two trials. In the first, there was no significant difference between amitriptyline and placebo, although patients experienced adverse effects with amitriptyline (Reference 81). In a second trial, amitriptyline was compared with cyproheptadine and placebo. The patients taking amitriptyline had no improvement in weight gain or depression scores. Patients taking cyproheptadine had improvement in both areas (Reference 82). Tricyclic antidepressants may cause several cardiac adverse effects including prolongation of the QT interval and sudden death in children and adolescents, so they should be used cautiously under direct medical supervision only.

The selective serotonin reuptake inhibitors (SSRIs) fluoxetine and citalopram have been studied in randomized controlled trials for AN. The SSRIs have efficacy for depression and obsessive compulsive disorder symptoms in children and adolescents, and they are

safer than the tricyclic antidepressants, but no studies using the SSRIs have shown patient improvements in weight restoration or eating disorder symptoms (Reference 59). In addition, there is a black box warning for using SSRIs in children and adolescents (see Pediatric Depression chapter), so these medications should only be used when risk outweighs benefits.

Most information regarding the use of antipsychotics for the treatment of AN has revolved around either case reports or case series. Although most studies with these agents have been completed in adults, there are some studies of atypical antipsychotics in children and adolescents. The most-studied atypical antipsychotics are olanzapine, quetiapine, risperidone, and aripiprazole.

Open-label trials and a case series have documented BMI improvements in children and adolescents taking olanzapine (References 83, 84). In addition, patient anxiety and agitation around eating meals was reduced. In randomized controlled trials using olanzapine in adults with AN, one study found improvements in weight gain and obsessional thinking. Weight gain, a common adverse effect of olanzapine, led to treatment refusal by half of the patients in the trial. Patients forced to gain weight without concomitant improvements in anxiety around gaining the weight typically have difficulty with treatment adherence. In the other trial, olanzapine and CBT did not separate out significantly from CBT alone (Reference 83).

Quetiapine has been used in two open-label studies of children (References 85, 86). In these studies, quetiapine improved depression and anxiety scores, but it did not significantly improve weight gain. In a case series of children and adolescents that used quetiapine for AN, patients reported improvements in body dysmorphism.

There are two case reports using risperidone in adolescents (References 87, 88). Patients did not show significant improvements in eating or weight gain in these reports, but they did show a decline in anxiety and obsessions surrounding food. There is currently a randomized placebo-controlled trial with risperidone for the treatment of AN in adolescents.

One case series of five patients with AN showed some improvements in anxiety and depression that may have led to improvements in BMI when aripiprazole was added to the patients' medication regimen. Patients, observed between 4 and about 40 months, seemed to have fewer obsessional symptoms and less distress around eating when aripiprazole was added (Reference 89). The National Institutes of Mental Health recently completed a clinical trial of aripiprazole for the treatment of AN.

Common adverse effects of antipsychotics include sedation and the potential for extrapyramidal adverse effects, which, in the long term, could lead to tardive dyskinesia. These agents can also cause metabolic syndrome, including hypertension, diabetes, and hyperlipidemia, and should be used with caution in children and adolescents.

Hormones have also been used in adolescents and adults for the treatment of AN. Growth hormone has been compared with placebo in adolescents with AN (Reference 90). In one study, the patients taking growth hormone became medically stabilized 10 days faster compared with patients not using growth hormone. There was no significant improvement in weight in any of these patients. Studies of testosterone use in adults with AN have shown mood improvement, but there were no specific improvements in weight compared with placebo (Reference 91).

One open trial using elemental zinc showed improvements in weight gain in patients with AN. Like the patients in the growth hormone study, patients receiving elemental zinc were hospitalized for about 7 days less than patients who did not receive zinc (Reference 92).

Summary

Medications should not be a first-line treatment in AN. Although medications may show some benefit in treating co-occurring depression, anxiety, or obsessive compulsive symptomatology, there is insufficient evidence that they improve weight gain or eating disorder symptoms. After medical stabilization and refeeding, nonpharmacologic therapy, especially FBT, is the most appropriate line of treatment.

Bulimia Nervosa

Bulimia nervosa, as opposed to AN, is often characterized by a loss of control in food intake (binge eating and purging). Whereas patients with AN attempt to take charge of their lives by limiting food intake, patients with BN often feel that they have lost control. Children and adolescents with AN who initiate binge and purge behaviors may eventually develop BN, although it typically occurs independently of AN.

Epidemiology

Although AN may occur in children and adolescents, BN is usually seen in adolescence or early adulthood, with a peak onset between age 15.7 and 18.1 years (Reference 93). Bulimia nervosa seldom occurs in premenarchal females. The lifetime prevalence of BN is 2.3%; the incidence of BN is 1% to 2% (References 94, 95). In one national study, less than one-third of all BN cases were recognized by a clinician because of the secretive nature of the disorder (Reference 95). Mortality rates

for patients with a diagnosis of BN are much lower than for AN at 3.9% and are often associated with suicidality and medical complications, primarily electrolyte imbalances (Reference 96).

Clinical Presentation

Bulimia nervosa is characterized by disinhibited eating of large quantities of food during a short amount of time and purging, either by self-induced vomiting, diuretics or laxatives, or all of these to reduce the potential weight gain associated with the binge. Although the amount of calories taken in a binge varies per individual, as many as 2000–5000 calories can be taken in during a discrete period. When individuals with BN binge, they typically do so until they experience significant abdominal discomfort. Vomiting helps decrease the stomach discomfort caused by the binge and, for some patients, allows them to continue the binge. Often, patients with this disorder are obese in childhood and early adolescence. The disorder itself is often not recognized by family, friends, or even health care professionals because the patient is typically within a normal weight range for age and height (Reference 56).

Patients with BN often hold over-idealistic views of what body weight and shape should be, leading them to feel conflicted about eating. Fluctuations in weight are common because of binge/purge behaviors (Reference 57).

Diagnostic Criteria

The diagnostic criteria for BN are listed in Table 2.

Risk Factors

Like those for AN, the risk factors for BN include having a family history of an eating disorder. Often, the parents of patients with BN are obese, and the relative risk of developing BN is 4.2% for first-degree female relatives with AN and 4.4% for first-degree relatives of patients with BN (Reference 64). A history of physical or sexual abuse and low self-esteem are also risk factors for this disorder. Personality traits such as impulsivity and self-harm are commonly seen in this population. Patients with BN often have a history of excess dieting, frequently skipping meals, and having dissatisfaction with their body image. Performers like models, actors, athletes, and jockeys in certain sports such as ballet, gymnastics, dance, running, wrestling, and racing are at greater risk of developing BN because of stringent weight and body shape requirements (References 97, 98).

Course and Prognosis

Bulimia nervosa has a chronic course with periods of recovery and relapse. Although the 5-year clinical recovery rate is 55% (Reference 96), as many as 46% will continue to have eating disorder symptoms 6 years after treatment. As stated previously, the mortality risk

Table 2. DSM-IV-TR Criteria for Bulimia Nervosa (Reference 63)

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
   1. Eating, in a discrete period (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period and under similar circumstances
   2. A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)

B. Recurrent inappropriate compensatory behavior to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise

C. The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice weekly for 3 months.

D. Self-evaluation is unduly influenced by body shape and weight.

E. The disturbance does not occur exclusively during episodes of anorexia nervosa.

Specify type:

Purging Type: during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
Nonpurging Type: during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas

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associated with BN is estimated to be 3.9% (Reference 36). Bulimia nervosa has a better outcome than AN, and a shorter illness before treatment is associated overall with improved outcomes. Premorbid obesity, poor family and peer relationships, and excessive exercise are all associated with poorer outcomes (Reference 99).

Treatment of BN

Initial goals in the treatment of BN include addressing any medical complications and decreasing and eventually eliminating binging and purging behaviors. It is important to provide patient education regarding adequate nutrition and to rectify incorrect thinking regarding body shape and size, eating, and weight. Treatment of co-occurring psychiatric conditions is imperative. Support systems should be used to prevent relapse.

Nonpharmacologic Treatment

Outside psychotherapy, much less is known about the nonpharmacologic treatment of BN compared with AN. There is much more evidence regarding the use of CBT in patients with BN. Cognitive behavioral therapy should be provided to patients on a weekly basis for 4–5 months (Reference 97). Interpersonal psychotherapy also has a role in helping patients with BN to work through interpersonal issues that may affect their eating disorder.

There are two controlled trials of FBT in adolescents and one trial of FBT in combination with CBT (Reference 100). Although the results are preliminary, they appear to be promising.

Pharmacologic Treatment

Antidepressants are the most studied medications for the treatment of BN. The first antidepressant trials used the tricyclic antidepressant desipramine, the tetracyclic antidepressant trazodone, and the monoamine oxidase inhibitor brofaromine (References 101–104). All of these trials were randomized controlled trials, and all found improvements in binging and purging behaviors distinct from their treatment of mood. These studies had small sample sizes and a short duration, and they did not have adequate follow-up trials. In addition, adverse effects of these medications include sedation, dry mouth, and weight gain. Monoamine oxidase inhibitor use is limited by dietary restrictions.

Bupropion was studied in one clinical trial, and although its use decreased binge and purge behaviors, it also caused grand mal seizures in 4 of 55 patients, and an advisory against its use in eating disorders was released (Reference 105). Fluoxetine is the only medication to be U.S. Food and Drug Administration (FDA) label approved for the treatment of BN. There are six randomized controlled trials supporting the use of fluoxetine for treating BN. Most of these trials support the use of fluoxetine 60 mg/day, a much higher dose than that used for the treatment of depression. Although binge/purge behaviors begin to respond in as few as 3 weeks, most studies suggest at least 8 weeks to allow a response, and treatment should be continued for at least 1 year (References 106–111). Both venlafaxine and fluvoxamine have shown some promise in treating BN. Use of an adequate dose for an adequate amount of time appears to be imperative for the use of any of the antidepressants in the treatment of BN (References 112–114). Topiramate, naltrexone, and ondansetron have all been used in small trials for the treatment of BN, and all three have been found successful in treating core symptoms. Further study in larger trials needs to be completed to recommend the role of these medications in the treatment of BN (References 115–118).

Summary

Although fluoxetine has an FDA label-approved indication for the treatment of BN, the research on fluoxetine was completed primarily in adults, which may not translate to treatment response in children and adolescents. Because information on children and adolescents is limited and because of the black box warning for antidepressant use in these age groups, antidepressants should be used with caution in this population. In addition, because CBT has been found beneficial in BN, medication is not considered first-line treatment. When medications are used, they should be used to help treat eating disorder comorbidities, and the patient should be closely monitored by a clinician.

Eating Disorders Not Otherwise Specified

Eating disorders not otherwise specified make up around 60% of all eating disorder diagnoses in children and adolescents (Reference 119). Most of the disordered eating seen in EDNOS is subsyndromal or an early presentation of the primary eating disorders AN or BN. Some of these subsyndromal cases will never meet the full diagnostic criteria for one of the eating disorders as defined by the DSM-IV-TR.

Binge eating disorder (BED) is currently categorized as an EDNOS. Provisional criteria have already been set for this disorder, and BED will most likely be a separate disorder in the DSM-V when it is published in 2013 (References 120, 121). The diagnostic criteria for BED are listed in Table 3.

Other eating disorders fall into the category of EDNOS. Four atypical eating disorders are usually reported: selective eating, food avoidance emotional disorder, food phobias (this includes functional dysphagia), and pervasive refusal syndrome.

Epidemiology

The prevalence of EDNOS is between 0.8% and 14%, depending on the symptoms and the way in which the disorder is defined (Reference 122). Patients who do not meet all the current criteria in the DSM-IV-TR for either AN or BN will fall into the category of EDNOS. If subsyndromal AN and subsyndromal BN were included with patients who meet the full diagnostic criteria, 45.7% of patients with EDNOS would be removed from that diagnostic group, leaving only 14.3% of patients who would actually be categorized as EDNOS. Of that 45.7%, 25.7% would be categorized as having a subsyndromal AN, and 20% would be categorized as having subsyndromal BN. Six percent of EDNOS would account for BED. The atypical eating disorders would make up 8.3% of the EDNOS. Unfortunately, insufficient research has gone into these atypical eating disorders to provide further epidemiologic characterization (Reference 122).

Clinical Presentation

Eating disorders are common in childhood and adolescents, but determining how to define them diagnostically has been a challenge. In the DSM-IV-TR, AN and BN have been defined on the basis of specific physical, behavioral, and cognitive parameters. Children and adolescents cannot meet the same criteria on the basis of these parameters. For example, an adult with AN is fully grown, and determinations can be made given a stabile height and BMI. Pubertal growth varies widely among children and adolescents. These independent variables make it difficult to determine specific DSM-IV-TR criteria related to weight on the basis of height. Currently, amenorrhea—defined as an absence of three menstrual cycles—cannot be determined in premenarchal girls, and it is difficult to determine in adolescents because it is common for menstrual cycles to be irregular during the first years after menarche.

Other challenges with defining AN and BN in children include their verbal and cognitive skills, including their ability to use abstract reasoning, all of which are required to make a diagnosis. Until adulthood, children and adolescents typically lack the insight needed to understand the deleterious effects of dramatic weight loss, for example, and the long-term effect on health or the behavioral consequences of such behaviors (Reference 122).

Despite these difficulties in matching the current diagnostic criteria to children and adolescents, there is no meaningful clinical difference between AN and BN and subsyndromal AN and BN.

Binge eating disorder is characterized by binging without the commensurate purging behaviors so that patients with this disorder gain a large amount of weight and are typically obese. Unlike the sex ratios with AN and BN, the ratios of males to females with this disorder are similar. Personality traits common to BED are low self-esteem and dissatisfaction with body shape and image. In addition to obesity, depression commonly cooccurs with BED (Reference 57).

The atypical eating disorder called selective eating refers to what is commonly called the picky eater. Such choosy eaters limit themselves to a small variety of foods and refuse to try new food items. There are thought to be two types of selective eating. The most common type is believed to be caused by never providing the young child a variety of foods and food textures. The secondary form of selective eating is thought to occur because of an event such as choking or vomiting. Personality traits associated with selective eating include shyness and sensitivity. Selective eating is common with pervasive developmental disorders (e.g., autism) and later in the development of AN (Reference 123).

Table 3. Provisional BED Research Criteria for Children (Reference 121)

A.	Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
	1. Food seeking in the absence of hunger (e.g., after a full meal)
	2. A sense of lack of control over eating (e.g., endorses that "When I start to eat, I just can't stop")
B.	Binge eating episodes are associated with one or more of the following:
	1. Food seeking in response to negative affect (e.g., sadness, boredom, restlessness)
	2. Food seeking as a reward
	3. Sneaking or hiding food
C.	Symptoms persist over a period of 3 months.
D.	Eating is not associated with the regular use of inappropriate compensatory behaviors (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of anorexia nervosa or bulimia nervosa.

BED = binge eating disorder.
Used with permission from Marcus MD, Kalarchian MA. Binge eating in children and adolescents. Int J Eat Disord 2003;34:S47–S57.

Food avoidance emotional disorders refer to an avoidance of most or all food. Children with food avoidance emotional disorders typically have an anxiety component to their illness, which presents as somatization. Children with this disorder often complain that "my tummy hurts," or they say they "are not hungry," or "cannot eat." Patients usually know that they are below weight norms and that it is not a positive experience for them. In addition to anxiety, these patients frequently experience depression, and later, they may be given a diagnosis of AN (Reference 123).

Food intake phobias usually occur in school-aged children who fear choking, vomiting, diarrhea, an allergic reaction to food, or other medical- or health-related concerns. Fear of choking associated with difficulty swallowing is called "functional dysphasia." Children with this phobia often choke or gag while eating (Reference 123).

Pervasive refusal syndrome is an absolute refusal to eat on the part of the child. Children may also refuse to walk, talk, or care for themselves. This atypical eating disorder is rare and is typically associated with posttraumatic stress, sometimes related to abuse. It has also been associated with learned helplessness (Reference 123).

Diagnostic Criteria

The diagnostic criteria for EDNOS are listed in Table 4.

Risk Factors

Risk factors for subsyndromal AN and subsyndromal BN are the same as for the full-spectrum disorders. Risk factors for BED include obesity in both first-degree family members and the patient, as well as low self-esteem, unhappiness with current body weight and shape, and a history of depression. Atypical eating disorders tend to occur in very young children and are associated with personality traits like shyness and sensitivity or emotionality; fear of choking; or vomiting, diarrhea, or an allergic reaction. Although rare, pervasive refusal syndrome may be associated with a severe stress or with physical, emotional, or sexual abuse.

Course and Prognosis

Subsyndromal AN and BN share the same course and prognosis as full-symptom AN and BN. Of importance, clinicians should recognize that subsyndromal eating disorders are just as important and as potentially dangerous to the patient as the full-spectrum disorders.

Although research on the course and prognosis of BED is limited, the prognosis appears good. In one 5-year study, 72% of patients made a full or partial recovery without treatment (Reference 124).

Research on atypical eating disorders is very limited, but some of it suggests that many children with these disorders will develop AN in middle childhood or early adolescence.

Treatment of EDNOS

Treatment of subsyndromal AN and subsyndromal BN should be similar to that of the full-spectrum disorders. The prepubertal onset of these disorders is usually at least as severe as the postpubertal forms of the disorders and may be more dangerous because of the lack of excess energy stores inherent in adults. Early interventions for the subsyndromal disorders provide the best outcome for patients. It is also important to remember that prepubertal forms of AN and BN are still associated with health risks, growth delays that may be permanent, and deficiencies in bone mass that lead to

Table 4. DSM-IV-TR Criteria for EDNOS (Reference 63).

The EDNOS category is for disorders of eating that do not meet the criteria for any specific eating disorder. Examples include:

1. For females, all the criteria for anorexia nervosa are met except that the individual has regular menses.
2. All the criteria for anorexia nervosa are met except that, despite significant weight loss, the individual's current weight is in the normal range.
3. All the criteria for bulimia nervosa are met except that the binge eating and inappropriate compensatory mechanisms occur at a frequency of less than twice a week or for less than 3 months.
4. The regular use of inappropriate compensatory behavior by an individual of normal body weight after eating small amounts of food (e.g., self-induced vomiting after the consumption of two cookies)
5. Repeatedly chewing and spitting out, but not swallowing, large amounts of food
6. Binge eating disorder: recurrent episodes of binge eating in the absence of the regular use of inappropriate compensatory behaviors characteristic of bulimia nervosa

DSM-IV-TR = *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; EDNOS = eating disorder not otherwise specified.

Used with permission from American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; text rev. Washington, DC: American Psychiatric Association, 2000.

osteopenia, as well as to cognitive impairments that may be permanent without treatment (References 124–128). Atypical eating disorders are poorly classified; thus, they have not undergone significant research to find treatments. Similar to AN treatment, establishing normal weight and eating patterns, teaching children and their families about healthy eating and nutrition, and treating co-occurring psychological problems are currently the best treatments for these disorders until they are better defined with established evidence-based research.

The goal of treating BED is to eliminate binging and help the patient lose weight in a healthy manner.

Nonpharmacologic Treatment

Like BN, both CBT and IPT are the most effective nonpharmacologic treatments for BED. Treatments target normalizing eating by using food diaries, problem solving, and reframing the ways in which patients view interpersonal issues.

Pharmacologic Treatment

The SSRIs, including fluoxetine, fluvoxamine, sertraline, citalopram, and escitalopram, together with the tricyclic antidepressant imipramine, have the most studies supporting their use in BED. The SSRIs appear to help decrease binge frequency, but they do not appear to affect weight loss. Medications studied for BED have been in short-term trials (less than 12 weeks), and these trials have experienced high dropout rates. Like SSRI use in BN, doses need to be in the high-end range to have an effect. The SSRIs do not appear to be better for BED than behavioral therapy (Reference 57).

Other medications found to help with binge eating in adults include topiramate, atomoxetine, zonisamide, lamotrigine, acamprosate, and orlistat (Reference 57). Adverse effects from these agents and recent warnings added to orlistat, in addition to the lack of studies in children and adolescents, indicate these treatments are not currently recommended as first-line treatments for pediatric BED.

Summary

Antidepressants, especially the SSRIs, improve BED by reducing binge eating. Antidepressants do not seem to cause significant long-term weight loss. Topiramate may also help with binging and weight loss, but further study must be completed to confirm the results of current trials.

Conclusions

The eating disorders AN, BN, BED, and EDNOS are all complex, serious, life-threatening disorders and should be viewed as such by clinicians. The mortality associated with eating disorders ranks highest among all the psychiatric disorders, especially regarding suicidality and starvation. Children and adolescents with eating disorders often do not meet all the diagnostic criteria in the current DSM-IV-TR. Work is being completed to remedy this in the DSM-V. Children and adolescents with subsyndromal eating disorders should be treated with the same degree of concern as individuals with full-spectrum eating disorders. Atypical eating disorders need further delineation and research to determine adequate treatments.

Medication trials are especially weak for the treatment of AN. Managing AN with medications alone is inappropriate. There is some evidence that, after medical stabilization and refeeding, FBT and CBT are beneficial and can decrease the risk of relapse.

The binging and purging behaviors of BN and the binging behaviors of BED respond to treatment with the SSRIs. Fluoxetine 60 mg/day is the only FDA label-approved treatment for BN. There is good evidence that CBT and IPT are effective for BN and BED. It is important to recognize that patients may often be nonadherent to medications because of the adverse effects associated with them.

Medication studies of the treatment of eating disorders in children and adolescents have several limitations. Many of these studies lack scientific rigor. Many studies are also poorly designed, have insufficient sample sizes, and lack sufficient power. As with most psychiatric research, there is a high dropout rate, which has an effect on study outcomes.

The long-term prognosis of eating disorders is improved if adequate treatment can be provided as early as possible. Recognition of these disorders by improving diagnostic criteria in the upcoming DSM will be a positive step toward new research for eating disorders in children and adolescents.

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CHAPTER 32

Substance Use and Addictive Disorders

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Learning Objectives

1. Describe the problems that arise from substance use and identify risk factors for addiction in children.
2. Discuss the intoxication effects and consequences of common substances of abuse.
3. Compare and contrast treatment approaches in pediatrics for substance use and addiction.

Abbreviations in This Chapter

AAP	American Academy of Pediatrics
ADHD	Attention-deficit/hyperactivity disorder
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders,* fourth edition
GABA	γ-Aminobutyric acid
GHB	γ-Hydroxybutyrate
LSD	Lysergic acid diethylamide
MDMA	Methylenedioxy methamphetamine
NRT	Nicotine replacement therapy
NSDUH	National Survey on Drug Use and Health
PCP	Phencyclidine
SUD	Substance use disorder
THC	Tetrahydrocannabinol

Introduction

The consequences of adolescent substance use disorders (SUDs) affect all realms of life. The harm to the adolescent and his or her family varies among biological, psychological, social, spiritual, and financial problems. The continuum of SUD varies between experimental use, abuse, and dependence, with the latter better referred to as addiction. Addiction is a chronic, neurobiologic disease of pathologic pursuit of reward and/or relief by substance use involving cycles of remission and relapse (Reference 1). Adolescent SUD is treatable, but it often becomes more difficult as it progresses to a chronic problem.

Epidemiology

Although several national surveys measure differing rates of substance use among adolescents, all show widespread use of alcohol and other drugs. The Youth Risk Behavior Survey (YRBS) is a national survey administered every 2 years to representative samples of 9th- to 12th-grade students. The 2009 survey showed that 72.5% of students had consumed at least one alcoholic drink in their lifetime. The present rate (defined as at least one drink in the previous 30 days) of alcohol use among high school students is 41.8% (Reference 2).

The National Survey on Drug Use and Health (NSDUH), an interview of individuals 12 years or older, has shown similar long-term trends, with lower prevalence rates compared with the YRBS. More than one-half (52.2%) of people 12–20 years old reported underage drinking at least once in their lifetime, and 27.2% consume alcohol currently. Limiting the age to 12–17 years resulted in a current alcohol use rate of 14.7% (Reference 3).

According to the NSDUH, the current drug use rate among those 12–17 years of age is lower than alcohol use at 10.0% (Reference 3). Marijuana is the most widely used substance, with a present rate of 7.3%. However, the YRBS showed a higher current use rate for marijuana of 20.8% (Reference 2). Marijuana, phencyclidine (PCP), and inhalants are drugs that adolescents often experiment with initially (Reference 3).

Another survey of students in the 8th, 10th, and 12th grades shows long-term trends similar to those in the previously mentioned studies. In the 2010 Monitoring the Future report, alcohol use continued to decline, whereas marijuana continued to rise among all three grades. The ongoing decline in cigarette use came to a halt in the lower grades, with both 8th and 10th graders showing increased smoking. About 1 in 14 (7.1%) 8th graders and up to 1 in 5 (19.2%) 12th graders are current smokers. These proportions are likely underestimated because the data do not include high school dropouts (Reference 4).

Neurobiology of Addiction

Addiction progresses over the course of three stages, with each stage corresponding to alterations to neurobiologic circuits in the central nervous system (Figure 1). The first stage, binge/intoxication, involves a reward pathway of the ventral striatum (location of the nucleus accumbens) from the ventral tegmental area. The neurotransmitters or neuromodulators with key roles in reinforcing the effects of drugs of abuse are primarily mesolimbic dopamine together with opioid peptide, γ-aminobutyric acid (GABA), and endocannabinoid. A

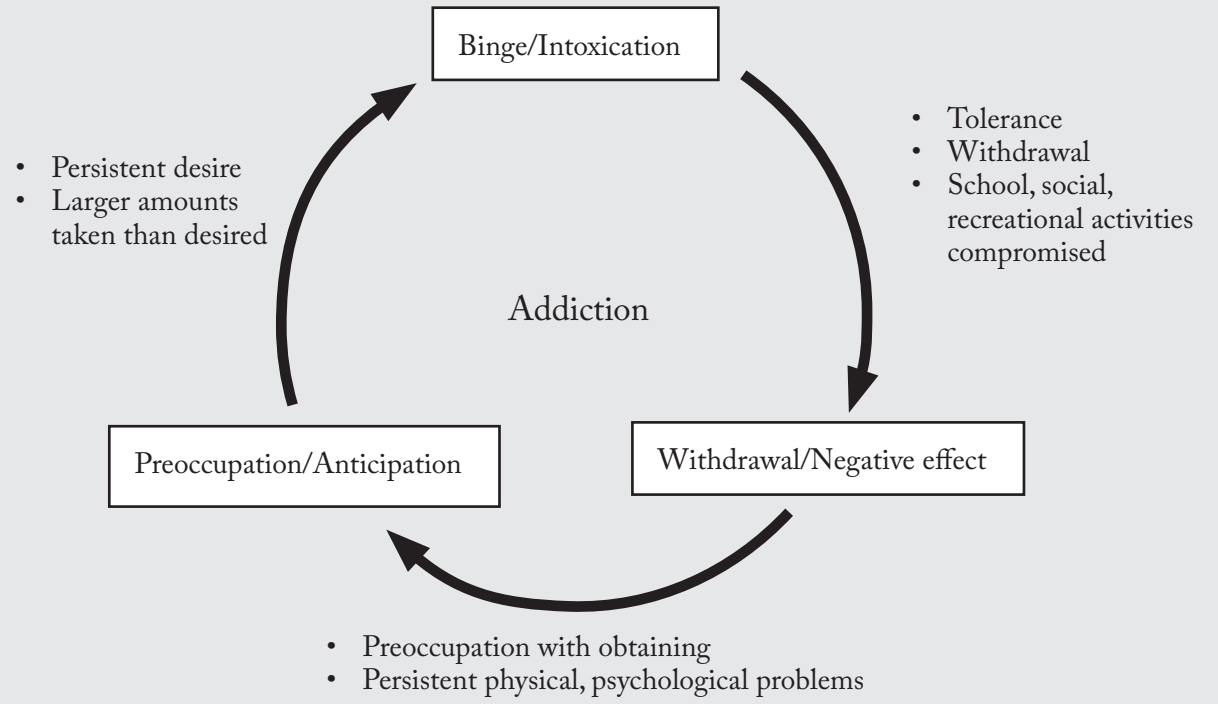


Figure 1. The addiction cycle. Diagram including different criteria for substance dependence incorporated from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed.

Adapted from Koob GF. Neurobiology of addiction. In: Galanter M, Kleber HD, eds. Textbook of Substance Abuse Treatment, 4th ed. Arlington, VA: American Psychiatric Press, 2008:3–16.

second stage of withdrawal/negative effect results from activation of the extended amygdala. The neurotransmitters thought to have a function in negative reinforcement are corticotropin-releasing factor, norepinephrine, and dynorphin. A widely distributed network, including the prefrontal cortex and hippocampus, mediates the third stage of preoccupation/anticipation. Glutamate is the main neurotransmitter involved in this phase of craving (Reference 5).

Adolescents may be particularly vulnerable to the exposure to alcohol and other drugs because the brain is still maturing throughout this period into young adulthood. Natural adolescent brain development involves a reduction in gray matter volume and enhancements in white matter, which are thought to support advances in cognition and behavior. Improved dopamine transmission occurs, mainly because of an increase in the density of connections in the prefrontal cortex. Neural consequences in adolescent substance users include poor white matter integrity as well as alterations in the prefrontal, hippocampal, and cerebellar structure. These are associated with deficits in neuropsychological functioning. These deficits may manifest as impairments in attention, information processing, spatial skills, learning and memory, and complex behaviors such as planning and problem solving. Adolescent SUDs during this developmental period increase the susceptibility to negative, chronic effects in all realms of life (Reference 6).

In general, a more developed limbic system, responsible for emotional and incentive processing, together with a lower-functioning prefrontal region involved in behavioral control, puts the adolescent at risk of poor decisions (Reference 6). Other risk or protective factors affecting adolescent SUDs are listed in Table 1. With the interaction of genetic and environmental influences, the more risk factors an adolescent has, the greater the chance of his or her substance use progressing to addiction.

Clinical Presentation and Diagnosis

Screening and Diagnosis

Several organizations recommend universal screening of adolescents for use of alcohol, tobacco, and other drugs at every health supervision visit and at appropriate acute care visits (References 7, 9, 10). Practice parameters (Reference 8) and consensus recommendations (Reference 11) suggest adolescents who exhibit

Table 1. Factors Influencing SUD in Adolescents

Risk Factors	Protective Factors
▪ Positive family history of addiction ▪ Early age of onset of regular use ▪ Drug-using peers or siblings ▪ History of mental health disorders ▪ History of sexual or physical abuse ▪ Parental crime ▪ Transition (divorce, change in school) ▪ College (alcohol use) ▪ Availability ▪ Advertising/media	▪ Parental approval ▪ Parental monitoring ▪ Two-parent home ▪ Family dining ▪ Perception of harm ▪ High religiosity ▪ Academic achievement ▪ College (tobacco use)

SUD = substance use disorder.
Adapted from References 3, 4, 6–8.

signs and symptoms of substance use receive an appropriate, confidential screening primarily focused on use patterns. Indicators for SUDs that reveal the need for a more comprehensive assessment include (Reference 11):

- Substance use indicators
  - Use of substances during childhood or early adolescence
  - Substance use before or during school
  - Peer involvement in substance use
  - Daily use of one or more substances
- Psychosocial indicators
  - Physical or sexual abuse
  - Parental substance abuse (including driving under the influence/driving while intoxicated)
  - Sudden downturns in school performance or attendance
  - Peer involvement in serious crime
  - Marked change in physical health
  - Involvement in serious delinquency or crimes
  - HIV (human immunodeficiency virus) high-risk activities (intravenous drug use, sex with intravenous drug user)
  - Indicators of serious psychological problems (suicidal ideation, severe depression)

A validated screen is available for adolescent SUD, and the American Academy of Pediatrics (AAP) recently published a universal algorithm for substance use, brief intervention, and/or referral to treatment (Reference 7). The National Institute on Alcohol Abuse and Alcoholism (together with the AAP) also recently published a quick tool for identifying adolescents at risk of alcohol-related problems (Reference 12).

Drug testing with consent from the adolescent is also a useful adjunct to screening for SUD. A negative screening result should be followed up with a reevaluation in 6 months for adolescents at high risk of a SUD.

The *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*), provides the formal criteria for adult SUDs (Reference 13). The diagnosis of substance abuse or dependence requires that a certain number of criteria be met in the previous year. These criteria do not accurately represent adolescent SUD for alcohol or cannabis, and refinement to consider abuse and dependence conjointly is expected in future editions (References 14–16). Therefore, many adolescents with SUD do not receive a diagnosis until adulthood.

Consensus recommendations (Reference 17) for adolescent SUD treatment, combined with a policy statement from the AAP (Reference 7), describe the stages of a substance use continuum. These include:

1. Abstinence
2. Use: Experimental or limited use with minimal consequences
3. Problematic use: Use in a high-risk situation (driving, babysitting), use with consequences, or use for emotional regulation (stress, depression)
4. Abuse: Regular use or abuse with several and more severe consequences
5. Addiction (dependence): Regular use for an extended period with continued severe consequences
6. Recovery: Return to abstinence, with a relapse phase in which some adolescents cycle through the stages again
7. Secondary abstinence

The coexistence of a SUD and another mental health disorder is often referred to as dual diagnosis. Common adolescent comorbidities associated with addiction are mood disorders, attention-deficit/hyperactivity disorder (ADHD), and conduct disorder. It is important to establish whether the SUD preceded the mental health condition or the reverse; the adolescent may either be experiencing a health consequence of the SUD or be self-medicating to treat the psychiatric illness, respectively.

Common Substances of Abuse

The more commonly abused drugs, together with common "street names" and health risks, are listed in Table 2. The signs and symptoms of intoxication or withdrawal are specific to the type of substance used and are described in the section below (References 13, 18). Intoxication is defined as the maladaptive behavioral or psychological change that develops after a recent ingestion of alcohol or other drugs. The syndrome after the cessation of (or reduction in) use that is heavy and prolonged to induce intoxication is known as withdrawal.

Cannabinoids

The active ingredient of marijuana, delta-9-tetrahydrocannabinol (delta-9-THC), is available from the Cannabis sativa plant together with other cannabinoids. The use of new synthetic cannabinoids that are marketed as herbal incense products is increasing in popularity. Delta-9-THC is a partial agonist at cannabinoid receptors, which regulate mood, motor control, perception (including pain perception), memory and cognition, appetite, sleep, reproductive function, and immune response (Reference 21).

Intoxicating Effects

- Conjunctival injection
- Increased appetite
- Dry mouth
- Tachycardia

Withdrawal Effects

- Irritability, anger, or aggression
- Nervousness or anxiety
- Insomnia
- Restlessness
- Depressed mood
- Decreased appetite or weight loss
- Stomach pain, shakiness or tremors, sweating, fever, chills, headache

The intoxicating effects of cannabis occur within 2 hours of use, and the withdrawal signs and symptoms may be apparent several days after last use.

Depressants

Alcohol acts as a central nervous system depressant by activating $GABA_A$. Opioid drugs interact with several opioid receptors, but the μ-receptor is primarily responsible for analgesia and dependence.

Alcohol

Intoxicating Effects

- Slurred speech
- Lack of coordination
- Unsteady gait
- Nystagmus
- Impairment in attention or memory
- Stupor or coma

Withdrawal Effects

- Autonomic hyperactivity (sweating or heart rate greater than 100 beats/minute)
- Increased hand tremor
- Insomnia
- Nausea or vomiting
- Transient visual, tactile, or auditory hallucinations or illusions
- Psychomotor agitation
- Anxiety
- Generalized tonic-clonic ("grand mal") seizures

Opioids

Intoxicating Effects

- Pupillary constriction
- Drowsiness or coma
- Slurred speech
- Impairment in attention or memory

Withdrawal Effects

- Dysphoric mood
- Nausea or vomiting
- Muscle aches
- Lacrimation or rhinorrhea
- Pupillary dilation, piloerection, or sweating
- Diarrhea
- Yawning
- Fever
- Insomnia

Withdrawal may develop after several hours to a few days after alcohol cessation and within a few minutes to several days after last opioid use or after administration of an opioid antagonist.

Stimulants

Stimulants (amphetamines, cocaine) work by either increasing the release or inhibiting the uptake of dopamine and norepinephrine. More recently, the use of synthetic stimulants, commonly marketed as "bath salts" and "plant food," has been increasing.

Table 2. Common Substances of Abuse

Substances	Street Names	DEA Schedule	Administration	Health Risks
Marijuana	Weed, blunt, chronic, dope, ganja, grass, green, herb, hydro, joint, bud, mary jane, pot, reefer, sinsemilla, skunk, smoke	I	Swallowed, smoked	Cough, frequent respiratory infections, anxiety, depression, schizophrenia
Synthetic marijuana	K2, spice, bliss, black mamba, Bombay blue, fake marijuana, fake weed, genie, Yucatan fire, skunk, moon rocks, zohai	I	Smoked	Unknown
Depressants				
Alcohol		Not scheduled	Swallowed	Increased risk of injuries, violence, fetal damage in pregnant women, depression, neurologic deficits, hypertension, liver and heart disease, fatal overdose
Opioids (oxycodone, hydrocodone)	Oc, ox, oxy, oxycotton, oxycet, roxy, hillbilly eroin, perc	II, III	Swallowed, snorted, smoked, injected	Respiratory depression and arrest, nausea, confusion, constipation, sedation, unconsciousness, coma
Heroin	Big H, black tar, brown sugar, chiva, dope, hell dust, horse, junk, negra, smack, thunder	I	Injected, smoked, snorted	Constipation, endocarditis, hepatitis, HIV, fatal overdose
Stimulants				
Amphetamines/ methylphenidate	Bennies, black beauties, crosses, hearts, LA turnaround, speed, truck drivers, uppers/JIF, MPH, R-ball, skippy, the smart drug, vitamin R	II	Swallowed, snorted, smoked, injected	Weight loss, insomnia, cardiac or cardiovascular complications, stroke, seizures Also, for amphetamines: tremor, loss of coordination, irritability, anxiousness, restlessness, delirium, panic, paranoia, impulsive behavior, aggressiveness
Mephedrone/ methylenedioxy-pyrovalerone (MDPV)/ methylone	Bath salts, bliss, blue silk, cloud nine, drone, energy-1, ivory wave, lunar wave, meow meow, ocean burst, pure ivory, purple wave, red dove, snow leopard, stardust, vanilla sky, white dove, white knight, white lightening	I (emergently classified)	Swallowed, snorted, smoked, injected	Unknown
Cocaine	Blow, bump, C, candy, charlie, coke, crack, flake, rock, snow, toot	II	Snorted, smoked, injected	Weight loss, insomnia, cardiac or cardiovascular complications, stroke, seizures, nasal damage from snorting
Methamphetamine	Batu, bikers coffee, black beauties, chalk, chicken feed, crank, crystal, fire, glass, go-fast, hiropon, ice, meth, methlies quick, poor man's cocaine, shabu, shards, speed, stove top, tina, trash, tweak, uppers, ventana, vidrio, yaba, yellow bam	II	Swallowed, snorted, smoked, injected	Weight loss, insomnia, cardiac or cardiovascular complications, stroke, seizures, irreversible neurologic damage, impaired memory and learning, severe dental problems
Nicotine		Not scheduled	Smoked, snorted, chewed	Chronic lung disease, cardiovascular disease, stroke, cancers of the mouth, pharynx, larynx, esophagus, stomach, pancreas, cervix, kidney, bladder, and acute myeloid leukemia, adverse pregnancy outcomes

(continued)

Table 2. Common Substances of Abuse *(continued)*

Substances	Street Names	DEA Schedule	Administration	Health Risks
Club Drugs				
MDMA	Ecstasy, adam, beans, clarity, disco biscuit, E, eve, go, hug drug, lover's speed, peace, STP, X, XTC	I	Swallowed, snorted, injected	Sleep disturbances, depression, impaired memory, hyperthermia
GHB (γ-hydroxybutyrate)	Easy lay, G, georgia home boy, goop, grievous bodily harm, liquid ecstasy, soap, scoop, goop, liquid X	I III	Swallowed Pharmaceutical preparation	Unconsciousness, seizures, coma
Flunitrazepam (Rohypnol)	Circles, forget-me pill, la rocha, lunch, mexican valium, money drug, R2, reynolds, roach, roche, roofies, roofinol, rope, rophies, row-shay, ruffies, wolfies	IV	Swallowed, snorted	Confusion, fatigue, impaired coordination, memory, judgment, respiratory depression and arrest
Dissociative Drugs				
PCP (phencyclidine)	Angel dust, boat, hog, love boat, peace pill	I, II	Swallowed, smoked, injected	Memory loss, difficulties with speech and thinking, depression, weight loss
Ketamine	Cat valium, Jet K, K, kit kat, purple, special K, super acid, super K, vitamin K	III	Injected, snorted, smoked	Anxiety, tremors, numbness, memory loss, nausea
Dextromethorphan	CCC, Dex, DXM, poor man's pcp, robo, robotripping, skittles, triple C, velvet	Not scheduled	Swallowed	Hypoxic brain damage from severe respiratory depression
Hallucinogens				
LSD (lysergic acid diethylamide)	Acid, blotter, blue heaven, cubes, dots, mellow yellow, window pane	I	Swallowed, absorbed through mouth tissues	Flashbacks, hallucinogen persisting perception disorder
Psilocybin	Magic mushrooms, purple passion, shrooms, little smoke	I	Swallowed	Flashbacks, risk of psychiatric illness, impaired memory
Salvia divinorum	Salvia, shepherdess's herb, maria pastora, magic mint, sally-D	Not scheduled	Smoked, swallowed, chewed	Unknown
Other				
Inhalants	Laughing gas, gluey, huff, poppers, rush, snappers, whippets	Not scheduled	Inhaled through nose or mouth	Cramps, muscle weakness, depression, memory impairment, damage to cardiovascular and nervous systems, unconsciousness, sudden death
Anabolic steroids	Arnolds, juice, gym candy, pumpers, roids, stackers, weight gainers	III	Injected, swallowed, applied to skin	Hypertension, blood clotting and cholesterol changes, liver cysts, hostility and aggression, acne, premature stoppage of growth; in males: prostate cancer, reduced sperm production, shrunken testicles, breast enlargement; in females: menstrual irregularities, development of beard and other masculine characteristics

DEA = Drug Enforcement Agency; HIV = human immunodeficiency virus; MDMA = methylenedioxymethamphetamine.
Adapted from References 19, 20.

Amphetamines and Cocaine

Intoxicating Effects

- Pupillary dilation
- Tachycardia or bradycardia
- Elevated or lowered blood pressure
- Perspiration or chills
- Nausea or vomiting
- Weight loss
- Psychomotor agitation or retardation
- Muscular weakness, respiratory depression, chest pain, or cardiac arrhythmias
- Confusion, seizures, dyskinesias, dystonias, coma

Withdrawal Effects

- Dysphoric mood
- Fatigue
- Vivid and unpleasant dreams
- Insomnia or hypersomnia
- Increased appetite
- Psychomotor retardation or agitation

Withdrawal may occur within a few hours (typical for cocaine) to several days (typical for amphetamines or related substances) after cessation from stimulants.

The AAP considers tobacco use a pediatric disease (Reference 22). Nicotine is primarily the addictive component in tobacco. Smoking and chewing tobacco increase the risk of pulmonary disease, cardiovascular disease, and various cancers. Withdrawal begins within 24 hours of last nicotine use and includes dysphoric or depressed mood; insomnia; irritability, frustration, or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; and increased appetite or weight gain.

Caffeine is likely the most widely used substance but is not included in the previous surveys of adolescents. Of concern are the effects of the energy drinks that contain unregulated amounts of caffeine and ingredients that lack evaluation in adolescents (Reference 23).

Caffeine

Intoxicating Effects

- Restlessness
- Nervousness
- Excitement
- Insomnia
- Flushed face
- Diaphoresis
- Gastrointestinal disturbance
- Muscle twitching
- Rambling flow of thought and speech
- Tachycardia or cardiac arrhythmia
- Periods of inexhaustibility
- Psychomotor agitation

Withdrawal Effects

- Headache
- Marked fatigue or drowsiness
- Dysphoric mood, depressed mood, or irritability
- Difficulty concentrating
- Flulike somatic symptoms, nausea, vomiting, or muscle pain/stiffness

The withdrawal symptoms occur within 24 hours after last caffeine use.

Club Drugs

Methylenedioxymethamphetamine (MDMA), commonly referred to as ecstasy, is frequently sold in combination with other drugs, often resulting in unpredictable effects when it is abused. Methylenedioxymethamphetamine works mainly by inhibiting the reuptake of serotonin. Common symptoms of intoxication include mild hallucinogenic effects, increased tactile sensitivity, empathic feelings, lowered inhibition, anxiety, chills, sweating, teeth clenching, and muscle cramping.

The other "club drugs," γ-hydroxybutyrate (GHB) and flunitrazepam, are typically used as either an adjunct to sleep or date rape. γ-Hydroxybutyrate acts at the GHB and $GABA_B$ receptors, and flunitrazepam, like other benzodiazepines, acts at the $GABA_A$ receptor. The intoxication and withdrawal effects of these substances mimic those of alcohol.

Dissociative Drugs

Although uncommon, PCP is one of the first substances with which adolescents may experiment. Phencyclidine works mainly as a glutamate receptor antagonist. Within 1 hour of use, vertical or horizontal nystagmus; hypertension or tachycardia; numbness or diminished responsiveness to pain, ataxia, dysarthria, muscle rigidity, seizures, or coma; and hyperacusis may occur. The actions of ketamine and high-dose dextromethorphan are similar to PCP in causing the dissociative feeling separate from one's body and environment.

Hallucinogens

Other hallucinogens are not separately listed for criteria in the *DSM-IV*. Lysergic acid diethylamide (LSD) is a partial agonist at serotonin receptors. Psilocybin, better known as mushrooms, has LSD-like properties. Salvia divinorum is a plant with potent activity at the κ-opioid receptors. In a state of full wakefulness and

alertness, perceptual changes occur (subjective intensification of perceptions, depersonalization, derealization, illusions, hallucinations, synesthesias) after recent use of a hallucinogen. Other signs that develop are pupillary dilation, tachycardia, sweating, palpitations, blurred vision, tremors, and incoordination.

Other Substances of Abuse

Inhalants are next to marijuana as the most common drug initially used by adolescents. Inhalants include solvents (paint thinners, gasoline, glues), gases (butane, propane, aerosol propellants, nitrous oxide), and nitrites (isoamyl, isobutyl, cyclohexyl). Intoxication from inhalants includes the following signs and symptoms: dizziness, nystagmus, incoordination, slurred speech, unsteady gait, lethargy, depressed reflexes, psychomotor retardation, tremor, generalized muscle weakness, blurred vision or diplopia, stupor or coma, and euphoria. Of primary concern is the risk of sudden sniffing death syndrome, which may occur with any use of inhalants (Reference 24).

Anabolic steroids and other performance-enhancing substances (protein supplements and creatine) have few to no intoxicating effects. However, the AAP strongly objects to the use of performance-enhancing substances because of the potential for adverse health problems and the lack of principle and fairness (Reference 25). Adolescent athletes who are "doping" are at risk of the many consequences listed in Table 2.

Polysubstance Use

The various substances previously described may become even more harmful and addictive when used in combination. Polydrug use causes additive or interactive effects. For instance, acute ingestion of marijuana and alcohol increases the effects of D-9-THC (Reference 26). A particularly dangerous combination is cocaine and alcohol because the liver combines these substances to produce cocaethylene (Reference 27). This new substance intensifies the effects of cocaine and is associated with a greater risk of sudden death than cocaine alone.

Treatment

Of the 1.8 million 12- to 17-year-olds who needed treatment for a SUD, only 150,000 (8.4%) received it (Reference 3). Thus, more than 1.6 million adolescents remained untreated for a SUD in 2009. It is extremely helpful to be aware of the community resources available for adolescents needing evaluation for and treatment of a SUD.

An important determinant of treatment is at which stage along the substance use continuum an adolescent is in. The following is a concise description of treatment suggestions for adolescents (References 7, 17).

1. Abstinence: Positive reinforcement, anticipatory guidance
2. Use: Promote patient strengths, encourage cessation, provide education about risks of using alcohol and other drugs
3. Problematic use: As previously stated plus brief intervention; consider breaking confidentiality
4. Abuse: As previously stated plus referral for comprehensive assessment and treatment
5. Addiction (dependence): As previously stated plus referral to subspecialty treatment; encourage parental involvement
6. Recovery: Positive reinforcement, support
7. Secondary abstinence: Positive reinforcement, support

Nonpharmacologic Therapy

Brief intervention may include education on the immediate consequences of even casual use, a recommendation for abstinence possibly with negotiation, and an agreement for follow-up.

The recovery stage has several treatment phases. The acute intervention motivating the adolescent to recovery may be followed temporarily by detoxification, depending on the substance(s) used and the use pattern, for managing withdrawal. The next phase of treatment is rehabilitation, in which combinations of individual, group, and family therapy and 12-step–based fellowships (e.g., Alcoholics Anonymous, Narcotics Anonymous) are strong components. Other nonpharmacologic therapies helpful to an adolescent in recovery are scheduled chores and recreational activities, school or vocational training, and contracts with outlined consequences (Reference 17). The transition period from inpatient and/or residential treatment back to home is often difficult, and treatment should include continuing care to prevent relapse. Finally, maintenance of recovery may require further therapy and 12-step work to support abstinence.

Pharmacologic Therapy

Pharmacologic therapy for SUD may be divided into medications used for:

- Intoxication to stabilize the adolescent
- Detoxification to manage the signs and symptoms of withdrawal
- Maintenance of recovery

Most medications are not approved by the U.S. Food and Drug Administration for adolescent SUD; therefore, the risk-benefit must be balanced before initiating pharmacologic therapy. Limited data on SUD treatment in adolescents exist, and often, management strategies are extrapolated from adult recommendations. Available dosing information for the drug therapies reviewed below is listed in Table 3.

The management of intoxication should focus on respiratory, cardiac, and neurologic stabilization, together with administration of an antidote when indicated and available. Life support to maintain cardiorespiratory function and fluid replacement for hydration may be necessary. Comatose adolescents at risk of aspiration may require intubation and ventilation. Adolescents exhibiting psychosis may need sedation and antipsychotics. Medications recommended for reversal are naloxone, given repeatedly as needed, for acute opioid intoxication and flumazenil for acute intoxication with benzodiazepines, including flunitrazepam but not GHB. Physostigmine may have a role in GHB toxicity (Reference 28). Decontamination of the gastrointestinal tract (by activated charcoal and gastric lavage) or clothes and skin (inhalant use) may be indicated. Other substance-specific problems are methemoglobinemia from inhalant intoxication, needing methylene blue treatment (Reference 24), and hyperthermia from MDMA, requiring management with cooling blankets, acetaminophen, and benzodiazepines for shivering or seizures.

Detoxification is uncommon for most substances, but depressants may require therapy to manage the signs and symptoms of withdrawal. Long-acting benzodiazepines, although seldom needed, together with vitamin replacement, are appropriate for treatment of alcohol withdrawal. Opioid detoxification is more complicated in adolescents than in adults, and use of opioid agonists may be indicated. Methadone is a full receptor agonist with no controlled studies in adolescents. Buprenorphine is a partial agonist approved for opioid dependence in those 16 years and older. A Cochrane review provides no conclusion regarding opioid detoxification from the two controlled trials using buprenorphine (Reference 29). The findings from these trials are that 12 weeks of buprenorphine-naloxone maintenance is more effective than 2 weeks of buprenorphine alone (Reference 30), and buprenorphine is more effective than clonidine (Reference 31) for opioid treatment. Clonidine is not routinely recommended for detoxification, but it may be used early on for control of early autonomic withdrawal symptoms.

Maintenance therapies may be considered in treatment-resistant adolescents for alcohol dependence (Reference 8). Acamprosate works by activating $GABA_A$ receptors and blocking glutamate receptors. It has been shown to increase abstinence over placebo in adolescents with alcohol dependence at 90 days (Reference 32). Naltrexone, an oral opioid receptor antagonist, was found to reduce alcohol consumption and craving in

Table 3. Medications for Management of Adolescent SUD (References 29–33)

Acute Intoxication	
Flumazenil	0.01 mg/kg (maximal dose 0.2 mg); repeat every minute to maximal cumulative dose 1 mg
Naloxone	2 mg; repeat every 2–3 minutes
Detoxification	
Buprenorphine	6–8 mg/day; decrease by 2 mg every 7 days or up to 14 mg/day, taper to 14 days
Clonidine patch	0.1 mg on day 1; add 0.1 mg on day 2; add an optional 0.1 mg on day 4. Remove all patches on day 7 and replace with 0.2-mg doses. Remove all patches on day 14 and replace with 0.1-mg doses. Remove all patches on day 21.
Methadone	0.05–0.1 mg/kg/dose every 6 hours; increase by 0.05 mg/kg/dose. Decrease interval to every 12–24 hours at 1–2 days. Taper 0.05 mg/kg/day.
Maintenance	
Acamprosate	666 mg in morning, 333 mg in afternoon, 333 mg in evening for 12 weeks
Buprenorphine	Up to 24 mg/day (and naloxone 0.5 mg) for 9 weeks and then taper to 12 weeks
Methadone	Flexible dosing daily for 16 weeks
Naltrexone	25–50 mg/day for 6 weeks

SUD = substance use disorder.

an open-label trial of adolescents (Reference 33). Ondansetron (Reference 34) and disulfiram (References 35, 36) have also been evaluated in adolescents but are seldom recommended over the above therapies for alcohol dependence.

The use of pharmacotherapy in adolescents with tobacco use disorder is controversial. Although nicotine replacement therapy (NRT) is safe, a Cochrane review found little evidence that such medications are effective in promoting abstinence among adolescent smokers. Moreover, the evidence does not support the use of bupropion either alone or as an adjunct to NRT (Reference 37).

Adolescents with a SUD and a co-occurring psychiatric illness may benefit from programs that provide treatment of both disorders. Medications for mental health disorders that are considered nonaddictive would be more appropriate treatments for adolescents with dual diagnosis. For instance, atomoxetine may be considered over stimulant medications for the treatment of ADHD in an adolescent who also suffers from a SUD. Drugs used in studies of adolescents with a coexisting SUD and another mental health disorder include fluoxetine or sertraline for depression and alcohol dependence (References 38–40), lithium for bipolar disorder and alcohol or other drug dependence (Reference 41), and bupropion for ADHD and nicotine dependence (Reference 42).

Monitoring and Prognosis

Toxicologic testing may be an important component in the ongoing assessment of substance use during and after treatment. However, the AAP does not recommend routine home- or school-based drug testing (Reference 43). The opportunity for detection from a urine drug test may be small because most substances, with the exception of marijuana, are fully excreted within 72 hours or less. Other important limitations are that standard panels do not detect some of the drugs, such as alcohol and inhalants, most often abused by adolescents, and false-positive results may occur, which require follow-up. Other monitoring parameters may include self-reported substance use, adherence to therapies, and behavioral changes.

Untreated adolescents who abuse substances will likely progress to having addiction in adulthood. Treatment may effectively lead to abstinence; however, relapse is common in adolescents. Instead of increasing shame or providing punishment, the emphasis should be on what adolescents can learn from the relapse. With continued treatment and encouragement to abstain from alcohol and other drugs, the adolescent may lead a full and healthy life.

Prevention

Early-use prevention targeting children and preadolescents is thought to be essential to reducing the risk of progression to later addiction. A document, published by the National Institute on Drug Abuse, outlines the following 16 research-based principles, which are important to the structure, content, and delivery of drug abuse prevention programs (Reference 44).

Risk Factors and Protective Factors

1. Enhance protective factors (parental support/modeling), and reverse or reduce risk factors (delay the age of initiation).
2. Address all forms of drug abuse (illegal and legal substances, over-the-counter medications).
3. Address drug abuse problem within the local community.
4. Be tailored to address risks specific to audience (age, gender, ethnicity).

Prevention Planning

5. Enhance parent-child relationships while developing, discussing, and enforcing family policies on substance abuse.
6. Occur as early as preschool
7. Target educational (academic failure) and emotional (early aggression) awareness for elementary children.
8. Target increasing academic (study habits) and social (peer relationships) competence for middle and high school students.
9. Be aimed for a general population at key transition points (elementary to middle school).
10. Combine at least two programs (community-, school-, and family-based) to be more effective.
11. Reach many settings (schools, faith-based organizations, media).

Prevention Program Delivery

12. Retain core elements (structure, content, delivery) while adapting to local community.
13. Be long term to reinforce content.
14. Train teachers in positive classroom management techniques.
15. Employ active learning.
16. Be cost-effective.

Conclusions

Alcohol and other drug use is common among adolescents, but progression to later addiction may be preventable. Screening along the substance use continuum, followed by the suggested treatment of brief intervention to referral, is an appropriate management strategy for adolescent SUD. At minimum, adolescents should be advised that even casual use of substances, regardless of amount or frequency, is likely illegal and has the potential for adverse consequences. For further information regarding adolescent SUD, visit the suggested resources listed in Table 4.

Table 4. Suggested Resources

Resources	Availability
National Institute on Alcohol Abuse and Alcoholism	www.niaaa.nih.gov
The Cool Spot	www.thecoolspot.gov
Alcohol Screening and Brief Intervention for Youth	www.niaaa.nih.gov/YouthGuide
National Institute on Drug Abuse	www.nida.nih.gov
NIDA for Teens	teens.drugabuse.gov
Substance Abuse and Mental Health Services Administration	www.samhsa.gov
Treatment locator	www.findtreatment.samhsa.gov
Office of National Drug Control Policy	www.whitehouse.gov/ondcp
Above the Influence	www.abovetheinfluence.com
Parents. The Anti-Drug	www.theantidrug.com
Partnership for a Drug-Free America	www.drugfree.org
American Council for Drug Education	www.acde.org
Mothers Against Drunk Driving	www.madd.org
Students Against Destructive Decisions	www.sadd.org
AAP Resources	
Parent Education Online on various substance abuse issues	http://patiented.aap.org/categoryBrowse.aspx?catID=5012
Healthy Children on substance abuse	www.healthychildren.org/English/ages-stages/teen/substance-abuse/Pages/default.aspx
A Bright Futures Handbook	http://brightfutures.aap.org/pdfs/Preventive%20Services%20PDFs/Screening.PDF
Policy Statement on substance use screening, brief intervention, and referral for treatment	Pediatrics 2011;128:e1330–e1340
Policy Statement on alcohol use	Pediatrics 2010;125:1078–87
Policy Statement on tobacco use	Pediatrics 2009;124:1474–87
Technical Report on tobacco use	Pediatrics 2009;124:e1045–e1053
Clinical Report on the role of the pediatrician in prevention, identification, and management of substance abuse	Pediatrics 2005;115:816–21
Self-Help Resources	
Alcoholics Anonymous for problem drinkers	www.alcoholics-anonymous.org
Al-Anon/Alateen for friends and families	www.al-anon.alateen.org
Narcotics Anonymous for addicts	www.na.org

AAP = American Academy of Pediatrics.

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CHAPTER 33

Pediatric Depression

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Learning Objectives

1. Recognize signs and symptoms of and diagnostic criteria for a Major Depressive Disorder (MDD) in children and adolescents compared to adults.
2. Identify screening tools used to detect depression in youths.
3. List the three main treatment phases of MDD and corresponding treatment goals.
4. Recognize the role of psychotherapeutic treatments for MDD in youths.
5. Compare and contrast pharmacologic treatments in regards to mechanisms of action, dosing, efficacy, and tolerability.
6. Explain the risk of new onset suicidality associated with antidepressant use in youth as well as the risk of untreated depression.

Abbreviations in This Chapter

AACAP	American Academy of Child and Adolescent Psychiatry
ADHD	Attention-deficit/hyperactivity disorder
CBT	Cognitive behavioral therapy
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision
ECT	Electroconvulsive shock therapy
MAOIs	Monoamine oxidase inhibitors
MDD	Major depressive disorder
PHQ-9	Patient Health Questionnaire-9 Item
SNRIs	Serotonin norepinephrine reuptake inhibitors
SSRIs	Selective serotonin reuptake inhibitors
TCAs	Tricyclic antidepressants

Introduction

Major depressive disorder (MDD) can occur in children as young as preschool age and is associated with an increased risk of morbidity and mortality. Psychotherapy and pharmacotherapy are the mainstays of treatment for pediatric depression. This chapter will highlight important concepts in the diagnosis and management of depression in children and adolescents and evaluate key studies and controversies surrounding the use of antidepressant therapy in this patient population. The clinical course and duration of depression in youths, together with a review of treatment phases and pharmacologic options, are also discussed.

Epidemiology of Pediatric Depression

MDD in Adolescents

According to the adolescent supplement of the National Comorbidity Survey Replication, the prevalence of *mood disorders*, a term used to describe both unipolar and bipolar disorders, in adolescents 13–18 years old is 14.3% (Reference 1). About 11.7% of those surveyed met the diagnostic criteria for an MDD or dysthymia (Reference 1). An estimated 50% of these adolescents developed a mood disorder before age 13 (Reference 1). The incidence of mood disorders was found to increase with progressing age, and it almost doubled in rate in adolescents from age 13–14 years (8.4%) to 17–18 years (15.4%) (Reference 1). Although the depression rate is equal in females and males before puberty, depression is twice as common in females as in males after puberty, which is consistent with the rates observed in adulthood (Reference 2). Although female adolescents have higher rates of mood and anxiety disorders, males show higher rates of behavioral and substance abuse issues (Reference 1). In addition, it has been found that depressive symptoms below the threshold for meeting diagnostic criteria for MDD in adolescents are predictive of a major depressive episode in adulthood (Reference 3).

MDD in Children

Major depressive disorder may present in children as young as preschool age (Reference 4). There is a lack of current epidemiologic data available regarding the prevalence of childhood depression; however, earlier studies have described a prevalence rate for preadolescents (6–11 years old) ranging from 0.6% to 2.7% (Reference 5). According to the Centers for Disease Control and Prevention's NHANES (National Health and Nutrition Examination Survey), there is a 3.7% prevalence of mood disorders in children 8–15 years old, with higher prevalence rates in girls and older children (Reference 6).

MDD and Suicide

Major depressive disorder is associated with an increased risk of morbidity and mortality (Reference 7). According to the National Center for Health Statistics, suicide was the fourth leading cause of death in 2007 in

children aged 10–14 years and the third leading cause of death in those aged 15–24 years (Reference 8). About 50% to 75% of children and adolescents who commit suicide have had a mood disorder, with major depression being the most common (Reference 9). Additional risk factors for suicide, as reported by the Centers for Disease Control and Prevention, include previous suicide attempts, family history of suicide, history of depression or other psychiatric disorder, substance abuse, stressful life event or loss, easy access to lethal methods, exposure to the suicidal behavior of others, and incarceration (Reference 10).

In a secondary analysis of the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT), predictors of suicidality and nonsuicidal self-injury were evaluated during a 28-week study in adolescents with major depression. The authors concluded that family dysfunction, high levels of suicidality, and recent self-harm (suicidal or nonsuicidal) increase the risk of future suicide attempts and that recent nonsuicidal self-injury is the strongest predictor of future nonsuicidal self-injury. The presence of these patient characteristics should alert clinicians to the increased risk of future suicide attempts or self-injurious behavior (Reference 11).

Although adolescent males are more likely to complete suicide (4 males to 1 female) as a result of using more lethal methods for suicide, females have a higher rate of suicide attempts (Reference 2). Suicide attempts are also increased in those with multiple psychiatric comorbidities (Reference 12). Around 40% to 90% of children and adolescents with MDD have at least one other psychiatric condition, with dysthymia and anxiety disorders (both at 30% to 80%), disruptive disorders (10% to 80%), and substance use disorders (20% to 30%) being the most commonly occurring psychiatric comorbidities (Reference 2). Because depression is strongly associated with suicidal thoughts and behaviors, it is recommended that clinicians evaluate for the presence of these symptoms and risk factors on initial presentation and subsequent assessments (Reference 7).

Etiology and Pathophysiology

The exact etiology of depression remains unknown but is thought to be caused by genetic, biochemical, and environmental influences (Reference 2). Twin studies support a genetic component to depression, with a concordance rate for a major affective disorder of 76% and 19% in monozygotic and dizygotic twins, respectively (Reference 2). Studies show that a family history of depression is a major risk factor for the development of depression in children (Reference 2). It was found that children of parents with an affective disorder had a 2.6 times greater rate of developing MDD than children whose parents had no disorder (Reference 13). In the STARD (Sequenced Treatment Alternatives to Relieve Depression) Child study, the relationship between remission or amelioration of maternal depression and its impact on psychiatric and social functioning in children was assessed (Reference 14). Women 25–60 years old and their biological children between age 7 and 17 were eligible for inclusion. This analysis showed that remission in maternal depression was associated with lower levels of internalizing (e.g., depression, anxiety) and externalizing (e.g., behavioral) problems in youths. In addition, remission of maternal depression predicted changes in mothers' expressions of warmth and acceptance, which led to changes in youths' tendencies to internalize symptoms. These findings suggest that short-term treatment with an antidepressant induces maternal remission of depression, thereby affecting the mother's expression of warmth and acceptance, leading to decreased depressive and anxiety symptoms in children.

According to the "monoamine hypothesis," one of the most researched theories on depression, depression results from a deficiency or imbalance in monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine (Reference 15). Supporting this hypothesis is that antidepressant medications enhance monoamine function, thereby treating symptoms of depression (Reference 15).

The pathophysiology of depression is likely caused by a variety of factors, with recent research focusing on molecular mechanisms of depression (Reference 15). Hypercortisolemia, BDNF (brain-derived neurotrophic factor), hippocampal neurogenesis, circadian rhythm changes, and functional and structural brain imaging are among the various proposed factors contributing to the pathogenesis of depression (Reference 15).

Additional risk factors for child and adolescent depression include psychosocial stressors (e.g., childhood neglect or abuse), psychiatric comorbidities (e.g., attention-deficit hyperactivity disorder [ADHD], anxiety), chronic illness (e.g., diabetes), female sex, hormonal changes during puberty, presence of serotonin transporter gene variants, and use of certain medications (Reference 16).

Diagnostic Criteria and Clinical Presentation

According to the *Diagnostic and Statistical Manual of Mental Disorder*, Fourth Edition, Text Revision (DSM-IV-TR), the diagnostic criteria for MDD in children and adolescents are similar to those in adults. To meet the diagnostic criteria for a major depressive episode, at least five of nine depressive symptoms must be present during the same 2-week period. At least one of the five symptoms must be depressed mood or anhedonia, defined as an inability to experience pleasure in normal pleasurable acts; however, an irritable mood may be

considered equivalent to either depressed mood or anhedonia in the pediatric patient population. Depressive symptoms should be present almost every day for most of the day and should include the following:

- Depressed or irritable mood or anhedonia
- Significant weight loss or weight gain or failure to make expected weight gains in children
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Difficulty concentrating or indecisiveness
- Recurrent thoughts of death

To further meet diagnostic criteria, these depressive symptoms must cause clinically significant distress or impairment in social, occupational, or other areas of functioning. In addition, the symptoms must not be caused by illicit drug use, a medication, a general medical condition, and/or bereavement (Reference 17).

Although the diagnostic criteria for depression in children and adolescents are similar to those for adults, some differences in the clinical presentation of depression may exist based on the youth's physical, emotional, cognitive, and social developmental stage (Reference 7). Because data are conflicting with respect to the symptom presentation of depression in children and adolescents, a database study of children and adolescents who were referred to an outpatient mood and anxiety disorders clinic was conducted (Reference 18). This study evaluated clinical characteristics of depression in this patient population. Adolescents with depression showed more hopelessness/helplessness, fatigue/lack of energy/tiredness, hypersomnia, weight loss, and suicidality compared with children with depression. Comorbid substance abuse/dependence was found to be more prevalent in depressed adolescents, whereas comorbid separation anxiety, oppositional defiant disorder, and ADHD occurred more often in children. A depressed or irritable mood in children was often associated with specific events or preoccupations compared with adolescents. Other depressive symptoms, including feelings of guilt, negative self-image, anhedonia, delusions/hallucinations, weight gain, increased appetite, anorexia, psychomotor agitation/retardation, social withdrawal, and insomnia, were observed to occur at similar rates in both children and adolescents.

Differential Diagnosis

The presence of specific medical conditions (e.g., hypothyroidism, mononucleosis, anemia, certain cancers, autoimmune disease, premenstrual dysphoric disorder, chronic fatigue syndrome) and psychiatric conditions (e.g., anxiety, dysthymia, ADHD, oppositional defiant disorder, pervasive developmental disorder, substance abuse) that may occur with or show symptoms similar to depression should be assessed before confirming an MDD diagnosis (Reference 7). The use of certain medications that may cause symptoms of depression, such as stimulants, corticosteroids, and contraceptives, should also be evaluated (Reference 7). Patients with bipolar disorder, a cyclic mood disorder characterized by alternating episodes of mania and depression, will often experience an acute depressive episode before any periods of mania, making it difficult to distinguish between unipolar and bipolar depression. About 20% to 40% of children and adolescents initially presenting with depression develop bipolar disorder within 5 years after the onset of depression (Reference 7). Characteristics associated with an increased risk of developing bipolar disorder in adolescents with MDD include early-onset depression, depression accompanied by psychomotor retardation or psychotic features, family history of bipolar or other mood disorders, and drug-induced mania (Reference 19). Hence, it is important to monitor for the presence of hypomanic symptoms, such as a decreased need for sleep, excessive talking, distractibility, and flight of ideas, which often tend to worsen with antidepressant therapy (Reference 19). See the Pediatric Bipolar Disorder chapter for more detailed information on this disorder in children and adolescents.

Screening for MDD

Although evidence supporting the use of depression-screening instruments in youths is limited (Reference 20), it is recommended that clinicians screen all children and adolescents for depressive symptoms using checklists derived from the DSM-IV-TR, clinician-based instruments, and/or child/parent depression self-reports (Reference 7). The patient evaluation should also include interviews with the child and parent(s) and an interview alone with the adolescent, if attainable (Reference 7). The Patient Health Questionnaire-9 Item (PHQ-9) is a self-administered depression-screening tool, based on DSM-IV-TR criteria, developed for use in adults in primary care settings (Reference 14). Its utility in screening for adolescent depression was recently highlighted. The PHQ-9 has greater sensitivity but lower specificity in detecting depression in adolescents compared with adults. Thus, the PHQ-9 is unlikely to miss detecting depression in adolescents; however, false positives, possibly caused by an overlap of symptoms among mental health disorders or subthreshold symptoms of depression combined with adjustment disorder, may occur, thereby warranting further inquiry by providers. A limitation of the PHQ-9 is that it does not include an item for irritability, a symptom of depression included

as part of the diagnostic criteria for MDD in youths but not adults. Therefore, providers may need to specifically inquire about the presence of irritability when screening for depression. Other instruments evaluated for use in adolescent depression screening in the primary care setting include the BDI-PC (Beck Depression Inventory–Primary Care Version), a 7-item self-rated questionnaire, and the PHQ-A (Patient Health Questionnaire for Adolescents), a 67-item self-rated questionnaire (References 20, 21). The SDQ (Strength and Difficulties Questionnaire) has been studied in youths 4–16 years old but has a lower sensitivity in detecting depression in youths (33% to 54% sensitivity) compared with the aforementioned instruments used to detect depression in adolescents (Reference 20). The Children's Depression Inventory, a 27-item self-rated scale, can also be used to assess for depressive symptoms in children 7–17 years old and is the most commonly used inventory for childhood depression (Reference 22). In addition, the CDRS (Children's Depression Rating Scale), a 16-item clinician-rated instrument based on parent, child, and schoolteacher interviews, can be used to determine the severity of depression in children aged 6–12 years (Reference 23).

Clinical Course and Duration

Five major terms are used to describe the clinical course of MDD: response, remission, recovery, relapse, and recurrence. Response is defined as significant improvement, usually considered a 50% reduction in symptom severity from baseline, during the initial or acute treatment phase. Remission is a period of at least 2 weeks and less than 2 months characterized by the presence of no or very few depressive symptoms (i.e., PHQ-9 less than 5). Recovery is defined as either an asymptomatic period lasting 2 months or more or the presence of no more than one or two depressive symptoms for at least 2 months. Relapse is an episode of depression during the remission period, and recurrence is the emergence of MDD symptoms during the recovery period (Reference 7).

A major depressive episode persists for about 7–9 months in clinically referred youths. Although around 90% of major depressive episodes remit within the first 1–2 years of onset, the likelihood of recurrence is between 20% and 60% and further increases to 70% after 5 years. Risk factors for recurrence include younger age at onset, increased number of past episodes, severe current episode, psychosis, and psychosocial stressors (Reference 7).

Treatment

The two main treatment options for pediatric depression include pharmacologic and/or nonpharmacologic therapy. The following factors should be considered when selecting treatment modality: age, cognitive development, symptom severity and duration, comorbidities, family history of medication response, family and social environment, impact on functioning, and suicide risk. Service availability and patient or family preference may further guide treatment selection. For instance, cognitive behavioral therapy (CBT) may be unavailable in the patient's geographic area, or the child's parents may object to medication treatment (Reference 7).

Psychotherapy

A meta-analysis published in 2006 of 35 randomized controlled trials showed that psychotherapy had only modest effects on adolescent depression compared with previous trials reporting substantial benefit from psychotherapy (Reference 24). The practice parameter for children and adolescents with depressive disorders published by the American Academy of Child and Adolescent Psychiatry (AACAP) in 2007 provides a brief review of studies assessing the effectiveness of psychotherapy in pediatric depression. The AACAP practice parameter states, "it is reasonable, in a patient with a mild or brief depression, mild psychosocial impairment, and the absence of clinically significant suicidality or psychosis, to begin treatment with education, support, and case management related to environmental stressors in the family and school." The American Academy of Child and Adolescent Psychiatry states that supportive therapy has been shown to be as effective as CBT or IPT (interpersonal psychotherapy). However, AACAP mentions that, in those with moderate to severe depression, chronic or recurrent depression, significant psychosocial impairment, suicidality, agitation, and/or psychosis, supportive therapy and case management are not usually effective and that specific types of psychotherapy or pharmacotherapy are warranted (Reference 7). Interpersonal psychotherapy focuses on the patient's social functioning and relationship with others, whereas CBT is centered on addressing inaccurate or negative thinking patterns or behaviors that contribute to the patient's emotional distress (References 25, 26). Although AACAP states that moderate depression may respond to CBT or interpersonal psychotherapy alone, it denotes that more severe depressive episodes generally require antidepressant treatment, either alone or in combination with psychotherapy. If monotherapy with psychotherapy or antidepressants is ineffective, AACAP recommends a combination of the two treatment modalities.

In the ADAPT study, 208 patients 11–17 years old with moderate to severe depression whose response to a psychosocial brief initial intervention failed were randomized to receive treatment with a selective serotonin reuptake inhibitor (SSRI) plus CBT or an SSRI alone (Reference 27). All patients received routine mental health services together with active clinical care. No difference in treatment effectiveness was observed at any

time. In moderately to severely depressed adolescents, the addition of CBT to an SSRI did not result in improved outcomes or prevent adverse events and was not cost-effective. The authors concluded that if psychosocial interventions do not elicit a response within 2–4 weeks, an SSRI should be prescribed. Thus, in patients with more severe depression undergoing psychotherapy but not responding to it, clinicians should have a low threshold for initiating antidepressant therapy.

Pharmacotherapy

There are four main antidepressant drug classes. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs) are older antidepressants that are not recommended for use in pediatrics because of their adverse effect profile, toxicity in overdose, and lack of data supporting their use in this patient population (Reference 28). The TCAs inhibit the reuptake of both serotonin and norepinephrine, thereby increasing serotonin and norepinephrine in the synapse. The MAOIs block monoamine oxidase, the enzyme responsible for the breakdown of monoamines, including serotonin, norepinephrine, and dopamine (Reference 29). Newer antidepressants include SSRIs, serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine. The SSRIs block the reuptake of serotonin, whereas the SNRIs block the reuptake of both serotonin and norepinephrine (Reference 29). Bupropion is a norepinephrine and dopamine reuptake inhibitor (Reference 29). Mirtazapine increases the release of norepinephrine and serotonin through presynaptic α_2-antagonism (References 29, 30). Mirtazapine also shows 5-HT2 and 5-HT3 antagonism, which is associated with decreased serotonin-mediated adverse effects, such as gastrointestinal disturbances or sexual dysfunction (Reference 29).

Most controlled studies have evaluated SSRIs for the treatment of pediatric depression. The U.S. Food and Drug Administration (FDA) label-approved SSRIs for acute and maintenance treatment of depression in adults including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. Although only fluoxetine and escitalopram are indicated for treatment of depression in pediatric patients, all the aforementioned SSRIs have some data supporting their use in this patient population (References 31–35). Fluoxetine is FDA approved for use in patients 8–18 years old, whereas escitalopram is FDA approved for use in patients 12–17 years old (References 36, 37). For the treatment of adult depression, recommended first-line therapies include SSRIs, SNRIs, bupropion, and mirtazapine (Reference 38). Although few studies exist evaluating the use of these agents for the treatment of depression in the pediatric population, there are some data supporting their use. In addition, although no SNRIs are FDA approved for use in pediatric depression, venlafaxine has efficacy data supporting its use for the treatment of adolescent depression (Reference 39). Moreover, some open-label trials support the use of bupropion sustained release (SR) and mirtazapine in adolescent depression (References 40, 41).

To further assist with treatment selection and sequencing, two multisite, randomized controlled trials have been published. The Treatment for Adolescents with Depression Study (TADS) was a randomized controlled trial of 439 outpatient volunteers aged 12–17 with an MDD diagnosis. Most patients included in this study were considered to have moderate to severe depression. For 12 weeks, this study assessed the effectiveness of fluoxetine in combination with CBT compared with treatment with fluoxetine or CBT alone, as well as the effectiveness of fluoxetine or CBT alone compared with placebo. Fluoxetine in combination with CBT produced the greatest improvement in depressive symptoms. Combination therapy also elicited an earlier treatment response compared with CBT or fluoxetine alone. Fluoxetine alone was more efficacious than CBT alone, and CBT was no more effective than placebo (Reference 33). Response rates at 12 weeks for fluoxetine with CBT were 71%, whereas fluoxetine alone produced a response in 60.6% of patients. About 43% of patients responded with CBT alone compared with a response rate of 34.8% with placebo. However, by week 36 of therapy, no significant differences in response rates were observed between treatments (86% combination therapy, 81% fluoxetine, 81% CBT) (Reference 42). Although high-risk suicidal patients were excluded from the study, about 29% of patients at baseline were described as having at least minimal to severe suicidal ideation. Suicidal thinking significantly improved in all of these patients at 12 weeks, with the greatest reduction occurring in the fluoxetine plus CBT cohort. In addition, there were no completed suicides in this study. By 36 weeks of treatment, it was found that patients treated with fluoxetine alone were more likely to show suicidal ideation and treatment-emergent suicidal events than were patients receiving combination therapy or CBT alone (Reference 42). Investigators concluded that fluoxetine alone or in combination with CBT hastens the improvement of depression compared with CBT alone and that CBT added to fluoxetine decreases suicidal ideation and treatment-emergent adverse events in adolescents.

The Treatment of SSRI-Resistant Depression in Adolescent trial (TORDIA) was a randomized controlled trial of 334 patients aged 12–18 years with a primary MDD diagnosis who did not respond to an adequate dose and duration (2 months) of an SSRI. Patients were randomized to 12 weeks of (1) a different SSRI; (2) venlafaxine, an SNRI; (3) a different SSRI plus CBT; or (4) venlafaxine plus CBT. It was found that CBT plus

a switch to either an SSRI (e.g., paroxetine, citalopram, fluoxetine) or venlafaxine produced a higher response rate (54.8%) compared with either medication alone (40.5%). No significant difference in response rates existed with venlafaxine (48.2%) compared with a second SSRI (47%). Although response rates were comparable, venlafaxine was not as well tolerated as the SSRIs. Skin problems occurred more often in patients in the venlafaxine cohort. Significant increases in diastolic blood pressure and heart rate were also observed in patients receiving venlafaxine. Therefore, because SSRIs were shown to be equally effective and better tolerated than venlafaxine, investigators concluded that patients whose response to initial SSRI therapy failed should be switched to another SSRI rather than to venlafaxine. No statistically significant difference in self-harm adverse events or suicidality between treatments was observed, and no subjects in this study completed suicide. Contrary to findings from the TADS, the addition of CBT to antidepressant therapy did not reduce suicidal adverse events. This may have been because patients in the TORDIA study had higher suicidality at baseline and underwent frequent and intense safety monitoring. Overall, given the results obtained in these two trials, combination therapy with CBT and an antidepressant may produce the greatest symptom improvement in adolescents; however, studies assessing the utility of combination therapy in children are lacking.

In a follow-up study of the TORDIA sample, remission and relapse rates were evaluated at 48 and 72 weeks from intake (Reference 43). Remission was defined as 3 weeks or more with one or no clinically significant symptoms and no functional impairment, and relapse was defined as 2 weeks or more with probable or definite depressive disorder. About 61% of youths reached remission by 72 weeks. Random treatment assignment did not affect remission rate or time to remission. Factors associated with higher rates of remission included less severe depression, shorter depressive episode, lower functional impairment, less non-suicidal self-harm behavior, and less drug and alcohol abuse. Of the 130 subjects who achieved remission by week 24, about 25% relapsed by 72 weeks. No statistically significant difference was observed between random treatment assignments. Only non-white race was associated with higher rates of relapse.

Treatment Phases

The three main phases of treatment for MDD are acute, continuation, and maintenance. The main goal of acute-phase treatment, which typically lasts 6–12 weeks, is to achieve symptom response and remission. Medication-related adverse effects typically occur shortly after therapy initiation, whereas symptom improvement is often not observed until at least 2–4 weeks of treatment at a therapeutic dose. Once remission is achieved, patients enter the continuation phase of treatment, which typically lasts at least 6–12 months. Continuation-phase treatment is recommended for all patients who have responded to acute-phase treatment, with the goal of this treatment phase being relapse prevention. It is recommended that the dose used to achieve remission be continued during the continuation phase of therapy. In a study evaluating continuation treatment and relapse prevention, patients 7–18 years old with MDD and responding to fluoxetine treatment at 12 weeks were randomized to receive fluoxetine or placebo for an additional 6 months (Reference 44). Patients treated with fluoxetine had lower rates of relapse and an increased time to relapse compared with placebo. This study supports the continuation of antidepressants for at least 6 months after remission is achieved.

Patients with at least two previous depressive episodes, one severe episode, and/or chronic episodes of depression may require maintenance therapy. Other patient-specific factors that should be considered when assessing the need for maintenance therapy include comorbidities, psychosocial stressors, and family psychiatric history. During the maintenance phase of treatment, the antidepressant is continued for an additional 1–2 years or longer. The therapy goal during this treatment phase is to reduce the risk of recurrence (Reference 7).

Regardless of the treatment phase, psychoeducation, supportive management, and family and school involvement are recommended. *Psychoeducation* is a term used to describe the education that family and the patient receive regarding the cause of depression, symptoms, course of the disease, available treatment options, adverse effects, and consequences of untreated depression. Supportive management consists of psychotherapy, which entails self-reflection, problem solving, and the learning of coping skills. Through family and school involvement, the disorder will be better understood, and treatment can be monitored more closely (Reference 7).

Treatment Guideline

In 2007, the Texas Children's Medication Algorithm Project published updated consensus guidelines focusing on medication management in pediatric depression, specifically in patients 6–17 years old. No recommendations for children younger than 6 years are provided, given the lack of evidence available. This publication makes no recommendations regarding combination therapies versus medication management alone, but instead, focuses on a stepwise approach to medication management in pediatric patients with depression significant enough to warrant medications, such as depressive symptoms causing impairment in social or school performance and/or risk of harm to the patient or others. Most studies have evaluated the use of SSRIs for

the treatment of pediatric depression. Therefore, it is recommended that patients receive treatment with an SSRI such as fluoxetine, sertraline, or citalopram in stage I of therapy if they have not received an antidepressant for their current depressive episode or if they have received an inadequate trial of an antidepressant. Of note, escitalopram was not yet indicated for the treatment of adolescent depression when this algorithm was created, which may explain why escitalopram is not specifically recommended for stage I treatment. Paroxetine is not recommended as first-line therapy because of the increased number of study dropouts caused by adverse effects (e.g., exacerbation of depressive symptoms, agitation, hostility, epistaxis) occurring in the children treated with paroxetine compared with placebo (References 45, 46). Most studies have evaluated fluoxetine for the treatment of pediatric depression. Therefore, fluoxetine has the most evidence to support its use, and it is thus considered the antidepressant of choice unless drug interactions, history of poor response, or family resistance preclude its use. Citalopram and sertraline are also considered reasonable treatment alternatives in stage I.

If the patient does not respond to SSRI treatment in stage I or is unable to tolerate the current SSRI, it is recommended that the patient be switched to a different SSRI, including fluoxetine, sertraline, citalopram, escitalopram, or paroxetine (adolescents only if switching to paroxetine). The new antidepressant should be cross-tapered with the initial antidepressant in patients not switching from fluoxetine. Fluoxetine does not need to be tapered because of its long half-life. Patients who experience adverse effects from the initial agent should have that antidepressant discontinued, and a new antidepressant should be initiated at a lower dose. For those showing partial response to the initial antidepressant, an augmentation agent can be added to the medication regimen. Augmentation permits partial responders to continue receiving benefit from the initial antidepressant and enables the targeted treatment of symptoms not responding to the initial agent. It is unclear which augmentation strategies are most efficacious and best tolerated in the pediatric patient population because of the lack of evidence available. Some augmentation strategies that have evidence for effectiveness in the adult population include bupropion SR and mirtazapine; thus, these agents are recommended as possible augmentation strategies for pediatric depression.

Patients who have not responded to at least two adequate SSRI trials move to stage III of therapy, during which time a different antidepressant class (e.g., bupropion, venlafaxine, mirtazapine, duloxetine) is recommended. The guidelines do not provide further recommendations for subsequent stages of treatment because of the lack of data available in the pediatric population.

In patients not responding to antidepressant therapy, the following factors should be evaluated: medication adherence, dose of antidepressant, duration of antidepressant trial, diagnosis (re-examine the appropriateness of primary diagnosis and evaluate for the presence of psychiatric comorbidities), and psychosocial stressors. It is also recommended that psychotherapy, specifically interpersonal therapy or CBT, be tried in patients who have not responded to other psychotherapeutic interventions. If psychotherapy has not previously been tried, it is advised that a trial of psychotherapy be recommended to the child and family (Reference 47).

In patients with severe depression that fails to respond to antidepressant trials, electroconvulsive shock therapy (ECT) should be considered. Electroconvulsive shock therapy entails sending electric currents to the brain to induce a seizure, which subsequently leads to neurotransmitter release. State statutes may differ regarding the age requirement for ECT. According to an executive summary published by AACAP, the administration of ECT in adolescents should be considered only if the depression is severe, persistent, and significantly disabling and if it has failed to respond to at least two adequate trials of pharmacologic agents that have been accompanied by other treatment modalities. Electroconvulsive shock therapy may be considered earlier in the treatment of patients who either cannot tolerate pharmacologic treatment or cannot physically take medications or in high-risk patients when waiting for a pharmacologic response may endanger their life (Reference 48).

The Texas Children's Medication Algorithm Project also provides information on treating pediatric depression in children with other psychiatric comorbidities including psychosis, anxiety disorders, ADHD, and other disruptive behavior disorders. A review of treatments for these conditions is beyond the scope of this chapter but can be found in the Texas Children's Medication Algorithm Project publication (Reference 47).

Dosing

No dose-response studies of antidepressants have been performed in pediatric patients (Reference 49). Antidepressant dosing in the pediatric population is thought to be similar to that in adults; however, some studies report that the half-lives of SSRIs (paroxetine, sertraline, citalopram) and other newer antidepressants (bupropion) in children are much shorter than in adults (Reference 50). These studies infer that antidepressants may need to be dosed twice daily; however, more studies are required to support this dosing recommendation (Reference 49). Thus, monitoring for the presence of withdrawal symptoms should occur, specifically 8–12 hours after the last dose (Reference 47).

Most antidepressants should be initiated at a lower dose than recommended for adults to minimize the occurrence of adverse effects. The dose should subsequently be titrated on the basis of efficacy and tolerability. The SSRIs and SNRIs are typically dosed once daily in the morning or evening with or without food. Because only escitalopram and fluoxetine are FDA approved for pediatric depression, specific dosing recommendations for other antidepressants in this patient population are lacking in the literature. Adolescents being treated with escitalopram should be initiated on a dose of 10 mg/day, which can be titrated to 20 mg/day after a minimum of 3 weeks. Those treated with fluoxetine should be initiated on 10 mg/day, which can be increased after a minimum of 1 week. Because lower-weight children tend to have higher fluoxetine plasma levels, it is recommended they be initiated on 5 mg/day (Reference 50). Because of the long half-life of fluoxetine compared with that of other antidepressants, patients having difficulty with medication adherence may benefit from using this agent (Reference 49). The extended-release formulation of venlafaxine is dosed once daily compared with the two or three times/day dosing of the immediate-release formulation (Reference 51). The dose of bupropion SR should not exceed 400 mg/day because of an increased risk of seizures associated with higher doses (Reference 52). In addition, immediate- and sustained-release formulation of bupropion should be administered twice daily, with no single dose exceeding 200 mg/day, to avoid high peak concentrations. To reduce seizure risk further, a gradual dose titration should be employed. In addition, bedtime administration of bupropion should be avoided to prevent insomnia from occurring. Conversely, it is recommended that mirtazapine be administered at bedtime because of its sedating properties; however, in adults, it has been found that the drowsiness and sedation observed at lower doses diminishes in frequency and severity with higher mirtazapine doses (Reference 53). Thus, in youths receiving higher mirtazapine doses at bedtime and experiencing insomnia, a switch to morning administration of mirtazapine may be warranted.

Table 1 shows the doses and dose ranges of antidepressants studied in pediatric depression trials, as well as the major metabolic pathways and half-lives of these agents. Of the antidepressants listed in Table 1, citalopram, escitalopram, fluoxetine, paroxetine, and sertraline are available in liquid dosage form (Reference 54). Mirtazapine is available as an orally disintegrating tablet and may be beneficial for use in children unable to swallow tablets and capsules (Reference 61). In children who have difficulty swallowing and who are prescribed venlafaxine immediate or extended release, the contents of the capsule can be sprinkled on a spoonful of applesauce and swallowed immediately without chewing (Reference 51). A glass of water should then be administered to ensure that all pellets have been swallowed. Bupropion SR is only available in tablet form and should not be crushed, divided, or chewed to minimize the risk of seizures (Reference 52).

Optimizing Pharmacotherapy

Therapy response should be assessed at 4-week intervals. It is recommended that the patient receive treatment with a therapeutic dose of an antidepressant for a minimum of 4 weeks, if tolerated. If, at 4–8 weeks, the patient shows minimal to no response to medication therapy, or for those unable to tolerate the antidepressant, the antidepressant should be discontinued, and a new antidepressant should be tried. Patients showing partial response to therapy at weeks 4–8 of treatment may benefit from an increase in dose, or, if the patient is already taking the maximum recommended dose, augmentation therapy may be used. In patients who continue to be partial responders at week 12 of therapy, the next stage of treatment should be tried (Reference 7). Patients with residual symptoms at week 12 are more likely to relapse during the next 6 months of treatment compared with patients having no residual symptoms at this time (Reference 44). Thus, the treatment goal should be remission of symptoms rather than response to therapy.

Drug Interactions

Fluoxetine, bupropion, and paroxetine are potent cytochrome P450 (CYP) 2D6 inhibitors, thereby predisposing these agents to significant drug interactions (Reference 62). Sertraline has been found to inhibit 2D6 in a dose-dependent manner, with doses greater than 150 mg/day causing moderate to potent 2D6 inhibition (Reference 62). Thus, plasma levels of medications metabolized by the CYP2D6 enzyme, such as TCAs and antipsychotics (i.e., risperidone or aripiprazole), may be increased, resulting in adverse effects and toxicity. Citalopram and escitalopram have minimal CYP enzyme activity and few drug interactions. The MAOIs irreversibly inhibit enzymes responsible for dopamine, norepinephrine, and serotonin metabolism. To prevent serotonin syndrome, MAOIs should not be given within 5 weeks of discontinuing fluoxetine or within 2 weeks of discontinuing other antidepressant agents. In addition, antidepressants should not be administered within 2 weeks after discontinuing an MAOI.

Adverse Effects

Overall, SSRIs and other antidepressants are well tolerated by the pediatric patient population (Reference 7). Common adverse effects associated with SSRIs and SNRIs include gastrointestinal disturbances, sleep changes (insomnia,

somnolence, vivid dreams, and nightmares), restlessness, diaphoresis, headaches, akathisia, appetite changes, and sexual dysfunction. These adverse effects are usually dose-dependent and typically resolve with time (Reference 49); however, many adverse effects can be treated by either lowering the antidepressant dose or switching to a different antidepressant (Reference 38). Venlafaxine has been associated with causing dose-related increases in blood pressure; thus, routine monitoring of blood pressure is recommended. Mirtazapine may cause an increase in appetite, weight gain, and somnolence (Reference 7). The use of bupropion is contraindicated in patients with a seizure disorder, in patients with a history of anorexia/bulimia, and in patients undergoing abrupt discontinuation of alcohol or sedatives. Antidepressants have also been shown to cause behavioral activation, characterized by impulsivity, irritability, agitation, and/or silliness in about 3% to 8% of patients (Reference 49). Antidepressants may also cause rare adverse effects such as bleeding and serotonin syndrome (Reference 7).

Withdrawal Symptoms/Discontinuation Syndrome

After the continuation or maintenance phase of treatment is complete, and if lifelong antidepressant therapy is unwarranted, antidepressants should be slowly tapered rather than abruptly discontinued to prevent the occurrence of withdrawal symptoms. Withdrawal symptoms, also referred to as *discontinuation syndrome*, include flu-like symptoms such as nausea, headache, light-headedness, chills, and body aches, together with neurologic symptoms such as paresthesias, insomnia, and "electric shocks" (Reference 38). Some patients may develop symptoms similar to those consistent with a relapse in or recurrence of a depressive episode (Reference 7). Withdrawal symptoms can occur after receiving antidepressant treatment for only 6–8 weeks and can begin as early as 24–48 hours after treatment discontinuation (Reference 7). Symptoms typically resolve without treatment during a 1- to 2-week period (Reference 38). To prevent the occurrence of withdrawal symptoms, it

Table 1. Antidepressant Dosing in Pediatric Depression Trials and Pharmacokinetic Parameters

Antidepressant	Ages Studied (years)	Starting Dose (mg/day)	Dose Range (mg/day)	Major Metabolic Pathway (Reference 54)	Half-life (Reference 54)
Selective Serotonin Reuptake Inhibitors (SSRIs)					
Citalopram (Celexa) (References 31, 55–57)	7–18	10–20	10–40	2C19, 3A4	24–48 hours
Escitalopram[a] (Lexapro) (Reference 37)	12–17	10	10–20	2C19, 3A4	27–32 hours
Fluoxetine[a] (Prozac) (Reference 36)	8–18	10–20	10–20	2C19, 2D6 3A4 for norfluoxetine (Reference 58)	4–6 days Active metabolite: 9.3 days
Paroxetine (Paxil) (References 34, 45, 55)	7–18	10–20	10–50	2D6	21 hours (Reference 59)
Sertraline (Zoloft) (Reference 35)	6–17	25	50–200	2C19, 2D6	26 hours
Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)					
Venlafaxine (Effexor) (Reference 39)	12–18	37.5	150–225	2D6	5 ± 2 hours Active metabolite: 11 ± 2 hours
Other Agents					
Bupropion SR (Wellbutrin SR) (Reference 40)	12–17	100	150–400 (administer in two divided doses if ≥ 300 mg/day)	2B6	12 ± 3 hours (Reference 60)
Mirtazapine (Remeron) (Reference 41)	12–18	30	30–45	1A2, 2C9, 2D6, 3A4	20–40 hours

[a]FDA approved for child and/or adolescent depression.
SR = sustained release.

is recommended that the antidepressant dose be decreased by no more than 25% per week, with tapering usually occurring during a 2- to 3-month period (Reference 47).

Antidepressants and Suicidality

In October 2004, the FDA issued a black box warning for all antidepressants, describing the increased risk of suicidal thinking and behavior in children and adolescents (younger than 18 years) with MDD and other psychiatric disorders when treated with antidepressants. This warning was extended in 2007 to include young adults up to age 25 (Reference 63). The black box warning recommends evaluating the benefits and risks associated with antidepressant therapy when considering antidepressants for use in this patient population. Because short-term studies did not show an increase in suicidality in adults older than 24 and actually showed a decrease in suicidality in adults older than 65, this warning applies only to patients younger than 25 years. Also mentioned in this warning is that depression itself is associated with an increased risk of suicide, making it difficult to determine whether suicidality is a result of antidepressant treatment or a consequence of the disease. After the first black box warning in 2004, antidepressant prescription rates decreased by 18% from July 2003 to July 2004, whereas teen suicide rates increased for the first time in more than a decade, highlighting the consequence of untreated depression (Reference 64). In a cohort study of depressed patients 10–18 years old initiated on antidepressant therapy, the risk of suicidal acts did not vary within the class of SSRIs or between antidepressant classes (SNRIs, TCAs, mirtazapine, nefazodone, trazodone), thereby supporting the inclusion of all antidepressant agents in the black box warning (Reference 65).

Regardless of whether suicidality is because of antidepressant therapy or the disease itself, health care providers should educate patients of all ages about the possibility of increased suicidal symptoms, especially early in treatment, and monitor patients for clinical worsening, suicidality, and unusual changes in behavior during the first few months of therapy and during dosage adjustments. The FDA guidelines specifically recommend that during the first 4 weeks of antidepressant treatment, the clinician should meet face-to-face with the patient at least once weekly. For the next 4 weeks of therapy, the FDA advises biweekly visits, followed by a visit at 12 weeks. Thereafter, the patient can be seen as clinically indicated. In addition, symptoms such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania may be indicative of suicidality. Thus, family and caregivers should be educated on the importance of monitoring for the presence of these symptoms and of the subsequent need to contact a health care provider, should any of these symptoms arise.

Conclusions

Major depressive disorder can present as early as childhood and is associated with an increased risk of morbidity and mortality. To restore optimal functioning and prevent recurrence, it is necessary to identify symptoms of depression early in their course and provide effective treatment through psychotherapy and/or pharmacotherapy. More studies are required to further evaluate the efficacy and tolerability of antidepressant agents as monotherapy or in combination with psychotherapy in the pediatric patient population. Because of the risk of suicidality associated with antidepressant use, close monitoring for clinical worsening, behavioral changes, and suicidality is recommended when initiating antidepressants in patients younger than 25 years.

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PART VI

Infectious Diseases/ Immunology

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CHAPTER 34

Neonatal Sepsis

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Learning Objectives

1. Distinguish the differences in the etiology and treatment strategy between early- and late-onset neonatal sepsis.
2. Describe the elements of a maternal history and clinical presentation of a neonate that would lead to a high index of suspicion for sepsis.
3. Design an appropriate individualized treatment regimen for neonatal sepsis.

Abbreviations in This Chapter

AMG	Aminoglycoside
ANC	Absolute neutrophil count
CLABSI	Central line–associated bloodstream infection
CNS	Central nervous system
CoNS	Coagulase-negative staphylococci
CSF	Cerebrospinal fluid
EOS	Early-onset sepsis
GA	Gestational age
GBS	Group B *Streptococcus*
GNR	Gram-negative rod
HSV	Herpes simplex virus
LOS	Late-onset sepsis
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PCR	Polymerase chain reaction
VLBW	Very low birth weight (less than 1500 g)

Introduction

An estimated 3.1 million neonates in the world die every year (Reference 1). Of these, almost one-fourth die of severe neonatal infections such as sepsis, meningitis, and pneumonia. Improvements in the quality of and access to maternal and neonatal health care and anti-infective therapy are critical to reducing neonatal mortality rates (References 2–4). Despite such improvements, surviving the transition from fetal to neonatal life remains a challenge; the risk of death during the neonatal period is significantly higher than at any other time in childhood and throughout most of adulthood (References 1, 5) (Figure 1). An important factor in this age-related death rate disparity is the underdeveloped fetal and neonatal immune response (Table 1). An infected neonate is insufficiently equipped to fight invading pathogenic organisms and thus can rapidly develop severe sepsis (References 6–10). The pharmacist caring for neonates must always be prepared to quickly initiate appropriate treatment when sepsis is suspected and to closely monitor the response to treatment.

Neonatal Sepsis: The Basics

Neonatal sepsis can be defined as the presence of signs and symptoms suggestive of systemic infection together with pathogenic organisms cultured from the blood (i.e., septicemia). When systemic infection is strongly suspected but cultures are sterile, the neonate can be considered to have "clinical sepsis." Although this general definition of sepsis is no different from that for infants, children, and adults, septic neonates present with unique signs, symptoms, and clinical histories compared with older patients (Table 2).

The classification of sepsis depends on the neonate's day of life. Early-onset sepsis (EOS) occurs in the first 3 days of life (Reference 15). Pathogens associated with EOS are acquired perinatally from the mother's genital-fecal flora during birth, or from a new-onset intrauterine infection near the time of delivery. Late-onset sepsis (LOS) presents after the first 3 days of life. The infecting pathogens in LOS can also be acquired from the mother during labor and delivery, but they are more commonly acquired postnatally from parents and other caregivers and from nosocomial sources, including health care workers (References 9, 10, 16). Bacteria are the most common pathogens in EOS and LOS. Fungi are more common in LOS than in EOS, particularly in very low-birth-weight (VLBW) preterm neonates (References 17, 18). Congenital infection occurs in utero before birth from transplacental transmission of viral or bacterial pathogens (Reference 16).

Initial treatment of neonatal sepsis uses antimicrobials directed at the presumed infecting pathogen(s) on the basis of the timing of illness onset, clinical presentation, presence of important risk factors, and local patterns of pathogen prevalence and antimicrobial susceptibility. If a pathogen is identified, treatment can be tailored on the basis of sensitivity testing. Supportive treatment of sepsis can include supplemental oxygen and ventilation, cardiovascular support, parenteral nutrition, and adjunctive immunoglobulin.

Table 1. Deficiency and Clinical Significance of the Neonatal Immune System (References 6–8)

Immune Function	Neonatal Deficit	Clinical Significance
T cell	Decreased dendritic cellular function Low circulating numbers Defective endocytosis Decreased expression of costimulatory molecules (e.g., CD40, CD80, CD86) Reduced pathogen-induced cytokine production	Impaired cell-mediated immunity to intracellular pathogens (e.g., HSV, CMV, *Candida, Toxoplasma, Mycobacterium, Listeria, Salmonella*) Reduced response to immunization
Humoral	Minimal plasma B-cell differentiation Limited, low-affinity IgM response to antigens Reliance on transplacental acquired IgG until 4–6 months of age Transplacental IgG minimal < 32 wk GA Decreased T cell–independent B-cell presence in marginal zone of spleen Weak response to bacterial capsular polysaccharides	Limited ability to defend against pathogen attack, particularly < 32 wk GA Increased susceptibility to *Streptococcus*, *Neisseria,* and *Haemophilus influenzae* type b infection Reduced response to immunization
Macrophage	Diminished activation from T cells Decreased production of some cytokines Decreased movement Reduced number of progenitor cells	Impaired capacity to kill intracellular pathogens
Granulocyte	Diminished precursor storage pool Reduced number of progenitor cells Decreased movement Impaired microbicidal mechanisms	Inadequate neutrophil quantity to respond to sepsis Neutropenia with severe infection because of exhausted supply Diminished activity against *Staphylococcus* and GNRs
Complement	Reduced complement levels	Limited opsonic activity
Skin	Stratum corneum and vernix caseosa absent < 28 wk GA, epidermal barrier not mature until 32–34 wk GA	Very preterm neonates vulnerable to nosocomial pathogen colonization and infection in NICU, exacerbated by routine procedures that disrupt skin

Note: Premature neonates generally have a greater degree of immune deficit in proportion to their degree of prematurity.
CMV = cytomegalovirus; GA = gestational age; GNR = gram-negative rod; HSV = herpes simplex virus; IgG = immunoglobulin G; IgM = immunoglobulin M; NICU = neonatal intensive care unit; wk = week(s).

Microbiologic Etiology

Different pathogens are responsible for EOS, LOS, and congenital infection (Table 3). Group B *Streptococcus* (GBS) and *Escherichia coli* are responsible for most EOS cases in the United States (Reference 15). The provision of intrapartum antibiotic prophylaxis has reduced the incidence of early-onset neonatal GBS disease in the United States to 0.34–0.37 cases per 1000 live births (Figure 2) (Reference 22). In VLBW neonates, gram-negative bacteria (mainly *E. coli*) are slightly more common, causing 54% of all EOS cases and 5.1 cases per 1000 live births. The mortality rate in premature (younger than 37 weeks' gestational age [GA]) neonates with *E. coli* EOS is 38%. Gram-positive bacteria comprise 45% of all VLBW EOS cases, with GBS accounting for 2.1 cases per 1000 live births (References 15, 23). In the developing world, neonatal tetanus remains prevalent in EOS, affecting about 20–80 of every 1000 live births and 2% of all neonatal deaths worldwide (References 2, 9).

Nosocomial pathogens such as staphylococci, enteric gram-negative rods (GNRs), and *Candida* spp. dominate the microbiologic causes of LOS (References 17, 19, 20). In the VLBW population, coagulase-negative

Table 2. Relevant Infection History and Clinical Presentation in Neonatal Sepsis (References 10–14)

Maternal/Fetal History	Neonatal Features
Chorioamnionitis or other peripartum febrile illness or infection	Premature, low birth weight
Urinary tract infection	Apnea, bradycardia spells
Group B *Streptococcus* colonization	Respiratory distress, cyanosis
Prolonged rupture of membranes	Increased oxygen/ventilation requirement
Meconium-stained amniotic fluid	Feeding intolerance, emesis
Traumatic delivery	Abdominal distension, bloody stools
Fetal distress	Temperature instability
No prenatal care	Hyper- or hypothermia
	Lethargy, hypotonia
	Hypertonia, convulsions
	Hypotension, hypoperfusion, oliguria
	5-minute APGAR score < 6
	Immature-to-total neutrophil ratio > 0.2
	Platelet count < 100,000/mm^3
	CRP > 1 mg/dL

CRP = C-reactive protein.

Table 3. Etiology by Timing of Infection (References 12, 15–17, 19–21)

Early-Onset Sepsis	**Common:** Group B *Streptococcus* (*S. agalactiae*), *E. coli*
	Less common: *Staphylococcus aureus*, CoNS, *E. faecalis*, other *Streptococcus* spp., *Ureaplasma urealyticum*, *Listeria monocytogenes, Haemophilus influenzae, Candida albicans*
Late-Onset Sepsis	**Common:** CoNS, *Streptococcus agalactiae*, *S. aureus, Escherichia coli, Enterococcus* spp., *Klebsiella* spp., *Pseudomonas aeruginosa*, *Enterobacter* spp., *Serratia marcescens, Candida* spp.
	Less common: Other gram-negative rods, anaerobes, viruses
Congenital Infection	Toxoplasma, *Treponema*, rubella, CMV, HSV, VZV

CMV = cytomegalovirus; CoNS = coagulase-negative staphylococci; HSV = herpes simplex virus; VZV = varicella zoster virus.

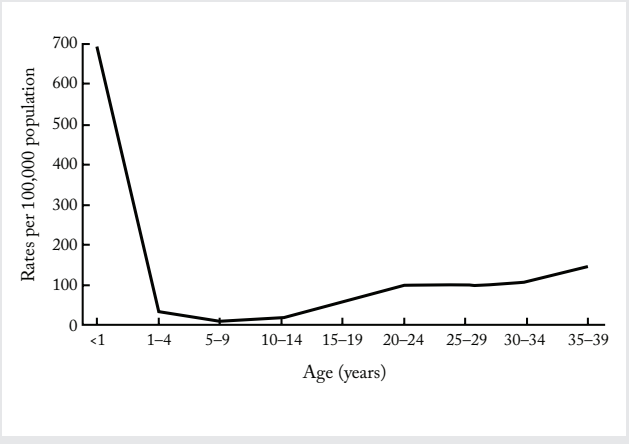


Figure 1. Age-specific death rates, United States, 2007 (Reference 5).

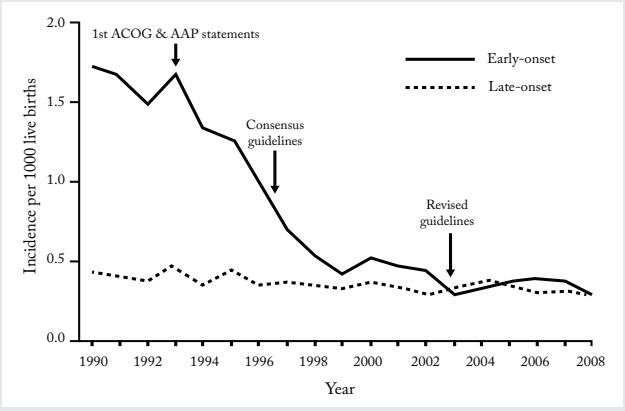


Figure 2. Incidence of early- and late-onset GBS sepsis in the United States (Reference 22).

GBS = group B *Streptococcus*.

staphylococci (CoNS) are the most common (48%) LOS pathogens, primarily from catheter-related infection (Reference 24). Among the GNRs, *Klebsiella* and *E. coli* are the most common (4% to 5%) (Reference 17). *Candida* and other fungi have been documented to occur in 12% to 14% of LOS cases (References 17, 18). Reported mortality rates are highest for LOS caused by *Candida* (30% to 50%) and GNRs (20% to 30%) and are lowest for CoNS and other gram-positive cocci (6% to 8%) (References 17, 25, 26). Negative neurodevelopmental outcomes such as vision and hearing impairment, cerebral palsy, and cognitive and motor developmental abnormalities are more likely to occur by 18–22 months of age in extremely low-birth-weight neonates who developed *Candida* or CoNS LOS than in noninfected controls matched for GA (References 27, 28).

Congenital infection may be caused by *Toxoplasma gondii*, cytomegalovirus, hepatitis B virus, herpes simplex virus (HSV), human immunodeficiency virus, Rubella virus, *Treponema pallidum*, *Mycobacterium tuberculosis*, and varicella zoster virus. Although newborns with congenital infections have several system disorders, some of which respond to antimicrobial therapy, their disease does not typically manifest as sepsis; hence, they will not be discussed in this chapter.

Clinical Presentation and Diagnostic Evaluation

Early-Onset Sepsis

Early-onset infection is among the most common illnesses responsible for neonatal hospitalization in the United States (Reference 29). However, the incidence of culture-proven EOS in North America is not high; there are about six or seven cases with a positive culture for every 1000 neonatal intensive care unit (NICU) admissions and one case for every 1000 live births. The incidence is highest among neonates born weighing less than 1500 g and is about 11 cases per 1000 live births (References 15, 30).

Specific maternal historical elements and clinical features of the neonate are highly suggestive of EOS (Table 2). The challenge in diagnosing EOS is that many other noninfectious neonatal conditions that present in the immediate postnatal period (e.g., asphyxia, congenital heart and other anatomic anomalies, metabolic disorders, maternal medication exposure, and idiopathic "poor transition") share similar symptoms. Thus, diagnosing EOS quickly and confidently on the basis of clinical findings alone is not always possible. Nevertheless, if a newborn presents with clinical or historical data strongly suggestive of EOS, a "septic workup" consisting of laboratory tests (blood culture, complete blood cell count with differential, and C-reactive protein level) and initiation of antimicrobial therapy will immediately follow. If the newborn is asymptomatic or only mildly symptomatic but with a maternal history possibly suggestive of EOS, laboratory testing and close monitoring for the appearance of sepsis are important. Treatment should commence only if either symptoms or laboratory results highly suggest sepsis (Reference 10).

A pathogenic organism detected in the blood confirms the diagnosis of sepsis. However, the lack of a positive result does not necessarily rule out sepsis. A false-negative blood culture may occur, especially when the mother is treated with antibacterial agents during labor for chorioamnionitis, prolonged rupture of membranes, or GBS colonization. In addition, bacteremia may be transient in the early stages of infection and thereby missed on a single blood culture, particularly if the quantity of blood sampled for culture was inadequate (less than 1 mL). The sensitivity of blood culture in diagnosing EOS is 50% to 80% (References 10, 12). Abnormal laboratory results such as elevated C-reactive protein levels, elevated immature neutrophils, and low platelet counts on their own lack sufficient positive predictive value (i.e., probability that the neonate has EOS when the results are abnormal) to establish the diagnosis of sepsis (Table 2 and Table 4). However, in the absence of a positive culture, several abnormal laboratory values may tip the diagnostic balance toward EOS if clinical features are present and other common causes of the symptoms are excluded. Algorithms for the diagnosis and empiric treatment of EOS are available (References 10, 22, 34). One algorithm is presented in Figure 3.

Meningitis and Pneumonia

Early-onset neonatal meningitis and bacterial pneumonia are focal infections that share the same clinical histories, symptoms, disease severity, and microbiologic etiology with EOS. Meningitis is a secondary infection caused by hematogenous delivery of the infecting organism(s) to the choroid plexus after primary bacteremia and sepsis. Pneumonia is a primary pulmonary focus of infection that can spread to the bloodstream and cause secondary bacteremia and sepsis.

Symptoms that suggest meningitis in term neonates include hyperthermia (e.g., axillary temperature greater than 37°C), high-pitched cry, apnea, hypotonia, hypertonia, irritability, convulsions, and a bulging fontanel. Because meningitis is a secondary infection that follows bacteremia, none of these symptoms need be present for meningitis to be considered if other symptoms or a maternal history suggestive of sepsis exists. In VLBW preterm neonates, fewer meningitis symptoms are present because of their immature immune, neuromuscular,

Table 4. Abnormal Laboratory Values Suggestive of Neonatal Sepsis or Meningitis (References 10, 11, 31–33)

Value	Suggestive	Normal Range
Blood		
WBC[a]	< 5	9–30[b]
ANC[a]	< 1.75	10–20
I:T	> 0.2	0.05–0.25
Platelet count[a]	< 100	150–400
CRP (mg/dL)	> 1	≤ 1
CSF		
WBC (cells/mm^3)	> 25	0–20
Protein (mg/dL)		
Term	> 100	40–80
Preterm	> 250	60–230
Glucose (mg/dL)	< 10	40–60

[a]10^3 cells/mm^3.
[b]5–20 after first week of life.
ANC = absolute neutrophil count; CRP = C-reactive protein; CSF = cerebrospinal fluid; I:T = immature-to-total neutrophil ratio; WBC = white blood cell (count).

and respiratory systems. Confounding this, symptoms such as apnea, respiratory distress, and hypotonia are common features present in very preterm infants and may not be related to infection. Given these difficulties in differentiating sepsis from meningitis on the basis of symptoms alone, and considering that negative blood culture results occur in 15% to 40% of neonatal meningitis cases (References 21, 32, 35, 36), it is recommended that all neonates with signs of sepsis undergo a diagnostic lumbar puncture for collection and analysis of cerebrospinal fluid (CSF) as a routine part of their sepsis evaluation (References 21, 22, 31).

The most common pathogens causing neonatal meningitis are *E. coli*, GBS, *Staphylococcus aureus*, viridans *streptococci*, and *Candida* (References 15, 31, 32). Positive identification of a pathogen from cultured CSF is limited by the potential for false-negative results because of pre-CSF sampling antibiotic use and inadequate sample volume (Reference 31). If CSF cultures are negative or unavailable, consideration should be given to other CSF findings. Cerebrospinal fluid elevations in white blood cell (counts) and protein content with low glucose concentrations relative to serum concentrations are associated with bacterial meningitis in neonates (Table 4). However, normal CSF findings do not necessarily exclude meningitis (References 32, 33, 35). Therefore, some experts recommend obtaining a CSF culture when a blood culture is performed and before antibiotics are initiated in all neonates suspected of having sepsis, regardless of the presence or degree of symptoms (References 11, 32). Such a recommendation is controversial because of the practical challenges associated with performing a lumbar puncture, such as technical expertise, parental consent, and preparation of an unstable patient, all of which can delay the initiation of antimicrobial therapy.

Early-onset neonatal bacterial pneumonia is acquired through aspiration of maternal flora or pathogens from an active intrauterine infection. The microbial etiology of early-onset pneumonia is therefore the same as that of EOS (see section on *Ureaplasma*, below). Respiratory distress dominates the clinical presentation, particularly in term neonates. Other signs of severe systemic illness may also be present and may initially be indistinguishable from, and considered part of, EOS. A chest radiograph, if available, may confirm the presence of early-onset bacterial pneumonia (Reference 37). If the neonate has been endotracheally intubated for respiratory failure shortly after birth, a positive tracheal aspirate culture can help distinguish infection from noninfectious respiratory disease (Reference 10). The remaining approach to management follows the same course as for EOS, with blood sampled for culture and cell count and initiation of empiric therapy.

Late-Onset Sepsis

A characteristic unique to LOS is the gradual onset of clinical deterioration compared with EOS. Increased oxygen or ventilation requirement, increased apneic events, feeding intolerance, bloody stools, lethargy, and hypotension are symptoms associated with LOS (Reference 38). Meningitis is more prevalent in LOS than in EOS (Reference 21). The pathogens that can cause LOS are varied, consisting of nosocomial bacteria, CoNS, and *Candida* (Table 3). Knowledge of the institutional pathogen distribution and antimicrobial sensitivity is therefore prudent in selecting an appropriate empiric therapy for LOS.

The diagnostic tools available for LOS are similar to those available for EOS. A urine culture is of greater diagnostic value in LOS, compared with EOS, and thus should be in the LOS diagnostic workup. A urine culture can be considered positive on the basis of three scenarios: the growth of a pathogenic organism from a urine sample collected by suprapubic needle aspiration; an organism quantity of more than 10,000 colonies/mL when collected by sterile catheterization; or an organism quantity of more than 50,000 colonies/mL when obtained by bag collection (Reference 39). The bag collection method is least reliable because of potential contamination during collection. Any symptomatic neonate with a positive urine culture should be considered

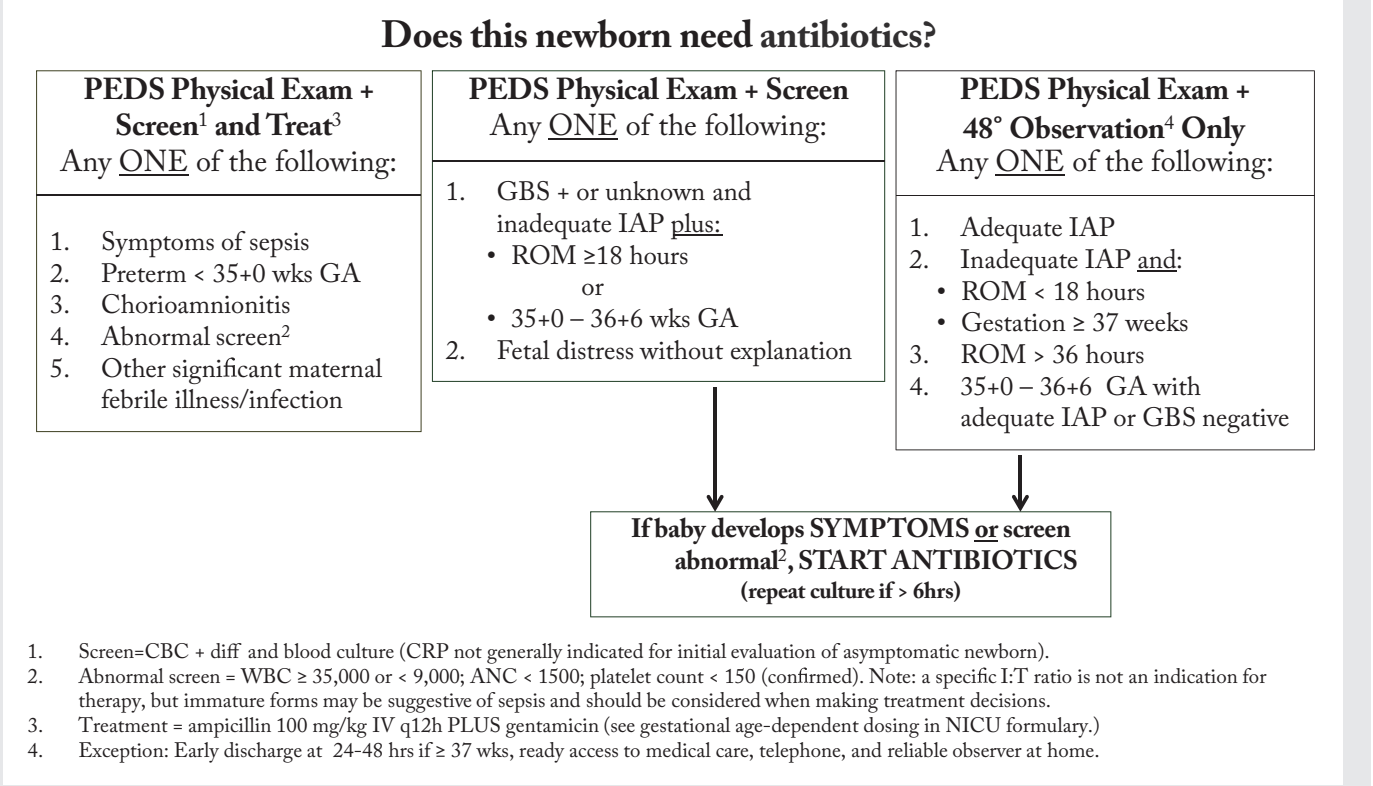


Figure 3. Early-onset sepsis diagnosis and treatment algorithm. (Adapted from the University of California, San Diego Infant Special Care Center Housestaff Manual, with permission)

ANC = absolute neutrophil count; bpm = beats per minute; CBC = complete blood cell count; CRP = C-reactive protein; GA = gestational age; GBS = group B Streptococcus; h/hr = hour(s); IAP = intrapartum antibiotic prophylaxis; I:T = immature-to-total neutrophil ratio; IV = intravenous(ly); NICU = neonatal intensive care unit; PEDS = Pediatrician; q = every; ROM = rupture of membranes; WBC = white blood cell (count)

to have septicemia necessitating treatment. Hematogenous infection of the kidney is more often the cause of a positive urine culture in an infected neonate compared with older infants and children, in whom the ascending route is more common (Reference 40).

Another distinction of LOS compared with EOS is the greater prevalence of central line–associated bacteremia (i.e., "line sepsis") due to the high frequency of catheter use for parenteral nutrition. Coagulase-negative staphylococci and other gram-positive organisms that are part of the normal neonatal skin flora are common causes of central line–associated bloodstream infection (CLABSI) and LOS (Reference 24). To differentiate CoNS infection from colonization or contamination, the same organism must be present in at least two separate blood cultures collected within 48 hours (Reference 41). In practice, two blood cultures are usually sampled at the same time during the initial LOS diagnostic workup; one blood sample is taken from the central catheter and the other from a peripheral venipuncture.

Treatment and Prevention

Although confirmed EOS is rare, occurring in 0.1% of all neonates, the use of empiric antibiotics for presumed EOS remains high (Reference 15). In fact, 12–28 antibiotic courses are initiated for every one case of confirmed or strongly suspected EOS (References 42, 43). In a large multicenter data set of more than 250,000 neonatal hospitalizations, around 70% of neonates were exposed to empiric EOS therapy (Reference 44). More than 50% of VLBW neonates receive antibiotics for presumed LOS during their NICU stay (Reference 17). Antibacterials are the most common medications used in neonates (References 44–46). It is thus a routine experience for the neonatal/pediatric intensive care pharmacist to participate in the initiation of empiric antibacterial therapy.

The explanation for this dichotomy between the high rate of empiric neonatal sepsis treatment and the low rate of actual confirmed sepsis is 3-fold: (1) the imprecision and unreliability of the sepsis diagnostic tools available, (2) the overlapping symptomatology of sepsis and other common neonatal diseases, and (3) the fast

onset of clinical deterioration and higher rate of mortality and neurodevelopmental morbidity in neonates who develop sepsis compared with those who do not (References 9, 10, 28). Because of this diagnostic uncertainty, early aggressive treatment is warranted to minimize significant morbidity and mortality.

The choice of empiric therapy for EOS or LOS targets the most likely pathogens (Table 5, Table 6, and Table 7). No single regimen has been found superior (References 13, 47, 48).

Early-Onset Sepsis

Intravenous ampicillin or penicillin plus an aminoglycoside (AMG) is the most common regimen for EOS (References 15, 47). This regimen provides coverage for the two of the most common pathogens, GBS and *E. coli*, and for less common infecting bacteria such as *Listeria*, *Haemophilus*, and other streptococci. The combination is also synergistic against GBS and *Listeria* (Reference 59). In the United States, GBS cultured from neonates with EOS is universally sensitive to both ampicillin and penicillin (Reference 15). Ampicillin is more commonly used in the United States for empiric EOS because of its commercial availability in a dose form appropriate for neonates (e.g., 250-mg and 500-mg vials), which allows rapid therapy initiation. Intravenous amoxicillin instead of ampicillin is commonly used for EOS elsewhere in the world where it is available (Reference 60). Gentamicin is the most commonly used AMG in the United States for EOS, whereas tobramycin, netilmicin, and amikacin are widely used elsewhere (Reference 61).

Table 5. Recommended Treatments for Severe Neonatal Infections (References 9–11, 20, 31, 49–56)

Infection/Etiology	Treatment[a]	Duration
Empiric EOS	Ampicillin + AMG/cefotaxime[b]	7–10 days for presumed sepsis[b] 10 days for confirmed sepsis 14 days for GBS meningitis 21 days for *Listeria* or GNR meningitis
GBS, *Listeria*	Ampicillin/PCN + gentamicin	
Escherichia coli[c]	Cefotaxime, AMG,[d] meropenem[e]	
Enterococcus	Ampicillin/vancomycin + gentamicin	
HSV	Acyclovir	21 days for disseminated or CNS 14 days if focus limited to SEM
Ureaplasma, Chlamydia trachomatis	Erythromycin, azithromycin	10–14 days of erythromycin 5 days of azithromycin
Mycoplasma hominis	Clindamycin	10 days
Bacteroides fragilis	Metronidazole, meropenem, chloramphenicol	Not well established; continue until clinical resolution
Tetanus	Metronidazole, PCN	10–14 days
Omphalitis	Clindamycin + gentamicin, pip-tazo, meropenem	10 days
Empiric LOS	Vancomycin + gentamicin or amikacin	Same durations as for EOS
Pseudomonas	Pip-tazo/ceftazidime + tobramycin, cefepime, meropenem	
CoNS, *Staphylococcus aureus*	Vancomycin, oxacillin	14 days[f]
Candida	Amphotericin B	21 days, may switch to fluconazole if sensitive
NEC	Vancomycin/ampicillin + gentamicin/cefotaxime ± metronidazole, meropenem	10 days or more depending on clinical response

[a]Commas separate alternatives; virgules separate alternatives within a combination regimen. Listed agents should be given intravenously. Some may be given intramuscularly if intravenous access is temporarily unavailable. See Table 5 and Table 6 for dosing recommendations.
[b]Controversial; see text.
[c]Or other enteric bacilli or *H. influenzae.*
[d]If meningitis ruled out.
[e]If ESBL or AMG/cefotaxime-resistant.
[f]5–7 days if central line removed.
AMG = aminoglycoside; CNS = central nervous system; CoNS = coagulase-negative staphylococci; EOS = early-onset sepsis; ESBL = extended-spectrum β-lactamase; GBS = Group B *Streptococcus;* GNR = gram-negative rod; HSV = herpes simplex virus; LOS = late-onset sepsis; NEC = necrotizing enterocolitis; PCN = penicil;lin; pip-tazo = piperacillin/tazobactam; SEM = skin, eye, and mouth.

Table 6. Treatment Dosing Recommendations for Therapeutically Monitored Antimicrobial Agents in Neonates and Young Infants (References 53, 57)

Antimicrobial (route)		Dose (mg/kg) and Frequency			Target Serum Concentrations	Comments
Aminoglycosides (IV/IM)		GA				
		≥ 37 wk	32–36 + 6 wk	< 32 wk		
Gentamicin-tobramycin	0–7 DOL	4 q24h	4 q36h	5 q48h	Peak 6–12 mg/L Trough < 2 mg/L	Use 0–7 DOL dosing for ELBW neonates (< 1000 g) until 10–14 DOL. Infuse over 30 minutes.
	> 7 DOL	4 q18h	4 q24h	5 q36h		
Amikacin	0–7 DOL	15 q24	15 q36h	15 q48h	Peak 20–30 mg/L Trough < 5 mg/L	
	> 7 DOL	15 q18h	15 q24h	15 q36h		
Vancomycin (IV)		SCr			Trough 5–15 mg/L	Add 0.2 to SCr if GA ≤ 28 wk Infuse over 2 h
		< 0.7	15 q12h			
		0.7–0.9	20 q24h			
		1–1.2	15 q24h			
		1.3–1.6	10 q24h			
		> 1.6	15 q48h			
Flucytosine (PO)		25 q6h			Peak 50–100 mg/L Trough 25–50 mg/L	Dose range 25–50 q6–24h
Chloramphenicol (IV/IM)		0–7 DOL	8–28 DOL			
		25 q24h	25 q12h		15–25 mg/mL	12.5–25 q6h if > 28 DOL

DOL = days of life; ELBW = extremely low birth weight; h = hour(s); GA = gestational age; IM = intramuscular(ly); IV = intravenous(ly); PO = orally; q = every; SCr = serum creatinine; wk = week(s).

Around 80% of *E. coli* causing EOS in the United States are ampicillin-resistant, while only 4% are gentamicin-resistant (Reference 15). To ensure adequate *E. coli* coverage when meningitis is suspected, cefotaxime should be added to empiric ampicillin/penicillin with AMG therapy, given the potential for poor CSF penetration of AMG. Treatment of confirmed meningitis is discussed in the Meningitis chapter. Treatment duration varies depending on the organism(s) isolated. For EOS without meningitis, treatment duration is 10 days, regardless of the infecting pathogen (Reference 11).

Some centers use cefotaxime in place of gentamicin for empiric EOS treatment (References 15, 62). This practice is controversial because of the increased risk of candidiasis correlated with the use of third-generation cephalosporins in the NICU, the reported rapid emergence of cephalosporin resistance after the initiation of routine cephalosporin use, and the retrospectively identified independent association of cefotaxime use with higher rates of death before NICU discharge (References 62–64). Advocates contend that cefotaxime use avoids inadequate empiric treatment of *E. coli* meningitis, particularly if regional ampicillin-resistant *E. coli* (or other GNR species) EOS prevalence is high. Cefotaxime use also avoids the need for therapeutic drug monitoring and the potential for gentamicin adverse effects such as ototoxicity and nephrotoxicity (References 65–67). Centers that use cefotaxime should follow infection control standards to prevent the spread of cephalosporin-resistant organisms and *Candida* and consider the routine surveillance of stool cultures to monitor rates of cephalosporin-resistant bacterial colonization.

When neonates with signs and symptoms strongly suggestive of EOS do not have a pathogenic organism cultured from blood, CSF, or a tracheal aspirate (if intubated), they are considered to have "culture-negative" or "clinical" sepsis. The recommended treatment of clinical sepsis is combination therapy with ampicillin or penicillin plus an AMG for 7–10 days (Reference 10). A 7-day course is only used if there is an initial and sustained clinical response to therapy. The optimal duration of antibiotics for presumed sepsis is not entirely known (Reference 68), and practices differ among centers. If there is no clinical improvement by the end of the first 48–72 hours

Table 7. Treatment Dosing Recommendations for Systemic Antimicrobial Agents in Neonates and Young Infants (References 53, 57, 58)

		Dose (mg/kg) and Frequency of Administration				
		Chronologic Age ≤ 28 days				
		Body Weight < 2,000 g		Body Weight ≥ 2,000 g		Chronologic Age > 28 Days
Antimicrobial	**Route**	0–7 DOL	8–28 DOL[a]	0–7 DOL	8–28 DOL	
Acyclovir	IV	20 q12h	20 q8–12h	20 q8h	20 q8h	20 q8h
Amphotericin B	IV	1 q24h	1 q24h	1 q24h	1 q24h	1 q24h
Amphotericin B-LB	IV	5 q24h	5 q24h	5 q24h	5 q24h	5 q24h
Anidulafungin[b]	IV	1.5 q24h	1.5 q24h	1.5 q24h	1.5 q24h	1.5 q24h
Azithromycin	PO,IV	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h
Caspofungin	IV	25/m^2 q24h	25/m^2 q24h	25/m^2 q24h	25/m^2 q24h	25/m^2 q24h
Cefazolin	IV, IM	25 q12h	25 q12h	25 q12h	25 q8h	25 q8h
Cefepime[c]	IV, IM	30 q12h	30 q12h	30 q12h	30 q12h	50 q8h
Cefotaxime[d]	IV, IM	50 q12h	50 q8–12h	50 q12h	50 q8h	50 q12h
Ceftazidime[d]	IV, IM	50 q12h	50 q8–12h	50 q12h	50 q8h	50 q8h
Clindamycin	IV, IM, PO	5 q12h	5 q8h	5 q8h	5 q6h	7.5 q6h
Erythromycin	IV, PO	10 q12h	10 q8h	10 q12h	10 q8h	10 q6h
Fluconazole	IV, PO	12 q24h	12 q24h	12 q24h	12 q24h	12 q24h
Linezolid	IV, PO	10 q12h	10 q8h	10 q8h	10 q8h	10 q8h
Meropenem[d]	IV	20 q12h[e]	20 q8h[f]	20 q8h[e]	30 q8h[f]	30 q8h
Metronidazole	IV, PO	7.5 q48h[g]	15 q24–48h	15 q24h	15 q12h	7.5[g] q6h
Micafungin	IV	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h
Oxacillin/nafcillin[d]	IV	25 q12h	25 q8h	25 q8h	25 q6h	37.5 q6h
Penicillin G aqueous[h]	IV	q12h	q8h	q12h (q8h)[h]	q8h (q6h)[h]	q6h
Pip-tazo	IV	80 q12h	80 q8h	80 q8h	100 q8h	100 q8h
Rifampin	IV, PO	10 q24h	10 q24h	10 q24h	10 q24h	10 q24h

[a]May use the longer dosing interval listed in extremely low-birth-weight (less than 1000 g) neonates up until 2 weeks of life.
[b]Loading dose 3 mg/kg.
[c]50 mg/kg/dose q8h for *Pseudomonas* infections.
[d]For meningitis, may double the dose; keep interval the same.
[e]Dosage for 0–14 d old.
[f]Dosage for ≥ 14 d old.
[g]Loading dose 15 mg/kg.
[h]Dose is 50,000 units/kg. If using for GBS meningitis: dose is 100,000 units/kg, and use the frequency in parenthesis if infant is > 2 kg.
DOL = days of life; GBS = group B *Streptococcus*; h = hour(s); IM = intramuscular; IV = intravenous; LB = lipid based; pip-tazo = piperacillin/tazobactam; PO = orally; q = every.

of empiric therapy and the suggestion of bacterial infection remains high, an undetected pathogen that is not sensitive to empiric therapy may be causing disease. Potential bacterial suspects in this situation are staphylococci, Enterobacteriaceae, and anaerobes. Changing treatment to vancomycin plus either cefotaxime, piperacillin/tazobactam, or meropenem is acceptable. Blood should be recultured before the new regimen is initiated.

HSV and *Ureaplasma*

Other pathogens to consider when the response to initial standard treatment of clinical EOS is lacking include HSV and *Ureaplasma*.

Disseminated neonatal HSV infection primarily involves the lung, liver, and brain, leading to pneumonitis, hepatitis, encephalitis, and pleocytosis. Presenting symptoms are similar to bacterial sepsis: temperature

instability, lethargy, poor feeding, convulsions, or respiratory compromise. Symptom onset can be early or late, but it is usually within the first 3 weeks of life. About one-third of HSV-infected neonates will not have a vesicular rash or conspicuous lesions in the eye or mouth, and there may be no history of known maternal HSV disease (Reference 49).

Diagnostic tests for neonatal HSV infection include the viral culture of blood, vesicular lesions (if present), and surface sites such as the conjunctiva, umbilicus, mouth, nasopharynx, and rectum. The CSF is also collected and analyzed by polymerase chain reaction (PCR) for the detection of HSV DNA; PCR is superior to culture for identifying HSV in CSF. Empiric treatment with intravenous acyclovir (Table 5 and Table 6) should be initiated after samples have been collected and should be continued until culture and PCR results are available. A positive culture or PCR result confirms the diagnosis of HSV infection and necessitates the continuance of intravenous acyclovir for 14–21 days (see Table 5). In neonates with central nervous system (CNS) infection, a repeat CSF collection for PCR analysis near the completion of the acyclovir course should be performed to document the absence of HSV. Without acyclovir treatment, the mortality rate for disseminated or CNS neonatal HSV infection is 50% to 85% by 12 months of age. With treatment, the mortality rate is 4% to 26% (References 49, 69, 70).

Potential complications of acyclovir include neutropenia and nephrotoxicity. Neutropenia occurs in 21% of acyclovir-treated infants, so the absolute neutrophil count (ANC) should be monitored two or three times/week. Acyclovir can be temporarily discontinued if the ANC falls below 500 cells/mm^3 and reinitiated when the ANC rises above this threshold (Reference 70). To minimize the risk of nephrotoxicity, appropriate hydration with intravenous fluids or enteral feedings should be used as clinical status allows, urine output should be strictly measured, acyclovir concentration for administration should be 7 mg/mL or less, and administration rate should not exceed 60 minutes. Care and maintenance of vascular catheter sites may be an ongoing challenge during the lengthy treatment course because acyclovir is incompatible with parenteral nutrition fluids and is a potent venous irritant. Regular monitoring for potential complications during an acyclovir course is recommended.

Ureaplasma spp. commonly colonize the female urogenital tract. These organisms can become pathogenic during pregnancy and cause maternal infections such as bacterial vaginosis, chorioamnionitis, and endometritis. Preterm labor and delivery is a potential outcome of maternal infection. Peripartum transmission from the vagina and cervix to the fetus can result in EOS, meningitis, and pneumonia in the neonate. *Ureaplasma* spp. lack a cell wall and require urea for energy. They cannot be detected by Gram staining, nor can they be grown in standard bacterial culture media. They are also osmotically fragile; tissue or blood samples require special handling after collection to be reliable (Reference 50). Isolating *Ureaplasma* from blood, CSF, or the lower respiratory tract is a challenge and is thus not routinely part of the EOS diagnostic plan. No established standards exist for treating early-onset *Ureaplasma* infection. However, experts recommend treating with a macrolide antibiotic if *Ureaplasma* is identified in the blood, CSF, or respiratory secretions (tracheal aspirate) of a neonate with EOS/pneumonia. Empiric treatment may be initiated before culture results if the respiratory disease is severe and the patient requires increased supportive care. Treatment may also be initiated if preterm delivery, premature ruptured membranes, and/or chorioamnionitis were maternal complications and if the organism has been identified in tissue cultures sampled from the amniotic fluid, placenta, or umbilical cord. Little evidence is available to guide optimal therapy for severe neonatal *Ureaplasma* infection or to show that treatment improves outcomes. Erythromycin is the most commonly used antibiotic for *Ureaplasma* infection (Reference 71). Several case series of preterm neonates indicate that erythromycin therapy usually achieves microbiologic cure, but improvement in short- or long-term clinical pulmonary disease does not always occur. Azithromycin use for neonatal *Ureaplasma* infection has not been reported; however, intravenous azithromycin has been safely used in this population for other indications (References 72, 73). See Table 7 for dosing recommendations.

Omphalitis

Omphalitis is an early-onset infection of the skin and soft tissues on and adjacent to the umbilical cord stump. Bacteria acquired during or after birth colonize the moist, necrotic stump and proliferate. Initial symptoms include local erythema, drainage, tenderness, periumbilical edema, and purulent discharge. If untreated, the infection can spread to the bloodstream by the umbilical vessels, causing sepsis and peritonitis, or it can extend to surrounding skin and subdermal tissues, causing abdominal wall cellulitis, lymphangitis, and necrotizing fasciitis. Initial symptoms suggestive of systemic spread are nonspecific, similar to those of EOS. Aseptic cord care after birth can prevent omphalitis. The incidence of omphalitis is believed to be lower in developed countries (1% to 2% vs. 6%) because of better cord care. Because omphalitis-related complications are so severe, prompt intervention with parenteral antibiotics upon identification of periumbilical erythema, cord edema, or purulent discharge is a standard of care. Broad-spectrum empiric therapy with clindamycin plus gentamicin, piperacillin/tazobactam, or meropenem will target

the likely pathogens: staphylococci, streptococci, enteric bacilli, *Pseudomonas*, and anaerobes (see Table 5). Mild disease, defined as cord erythema with no evidence of local symptoms, may be treated with the local application of alcohol, antibiotic ointment, and drying of the affected area (References 55, 56).

Late-Onset Sepsis

Treatment of LOS follows general principles similar to those for EOS. Empiric therapy targets the most likely organisms, including CoNS and other staphylococci, Enterobacteriaceae, and *Candida*, on the basis of local patterns of pathogen prevalence and sensitivities. Examples of recommended empiric regimens and drug dosing are listed in Table 5, Table 6, and Table 7. Treatment is tailored on the basis of culture and sensitivity results.

Neonatal Candidiasis

Candida albicans and *Candida parapsilosis* are responsible for causing 12% of LOS episodes and 20% of LOS-related deaths in VLBW neonates (Reference 17). The skin and gastrointestinal tract of neonates can become colonized with *Candida* spp., which can then opportunistically invade the bloodstream by gut translocation or through central venous catheters. Early exposure to cephalosporins and extreme prematurity (GA younger than 28 weeks) are known risk factors. Clinical presentation of late-onset fungal sepsis is generally the same as for bacterial LOS. Hyperglycemia and thrombocytopenia are also prevalent features. The kidney and urinary tract are among the most common sites of infection in neonatal disseminated candidiasis. Because of this potential for a renal focus of infection, conventional amphotericin B, which readily distributes to the kidney, is the treatment of choice for LOS from presumed or confirmed candidemia (References 74–76). Amphotericin B is not associated with nephrotoxicity in neonates at the same rates as in adults. Several case series and open-label prospective studies have examined amphotericin B efficacy and safety in neonates. Most report nephrotoxicity (elevated serum creatinine or oliguria) rates between 0% and 15% (References 77–82). A small prospective study comparing amphotericin B with fluconazole reported that only 1 of 11 neonates exposed to amphotericin B experienced mild renal impairment (Reference 83). One large study examined the nephrotoxic effects of amphotericin B in neonates during a 14-year period. Only 16% of 92 neonates showed a significant increase in serum creatinine during amphotericin B therapy. Most cases (94%) resolved despite the continuation of amphotericin B (Reference 84). In clinical practice, it is difficult to differentiate the cause of increased serum creatinine or decreased urine output. It may be related to amphotericin B or to the neonate's underlying renal infection and/or hemodynamic instability from severe sepsis. Switching to lipid-based formulations of amphotericin B to avoid nephrotoxicity is not recommended because of the potential for reduced distribution to the presumed renal infection site. Lipid formulations have also not been shown to be less nephrotoxic in neonates compared with conventional amphotericin B (References 85, 86). A conservative approach in the face of renal dysfunction during amphotericin B therapy is to prolong the dosing interval to every 48 hours if the serum creatinine is greater than 1.5 mg/dL or if it is rising more than 0.3 mg/dL per day. Use of a lipid-based amphotericin B formulation is justified if *Candida* infection outside the kidney or urinary tract (e.g., cardiac, CNS) is present or if a non-*Candida* fungal pathogen is identified (Reference 52).

The biggest challenge for the pharmacist assisting in the care of a preterm neonate receiving amphotericin B is drug administration. Amphotericin B is a known venous irritant and should ideally be administered by a central catheter. It also requires a 2- to 4-hour infusion and is not compatible with parenteral nutrition. A sick premature neonate usually does not receive enteral feedings; hence, discontinuing parenteral nutrition intake for 2–4 hours during amphotericin B administration is challenging. To solve this nutritional dilemma, amphotericin B should be prepared in a concentration and volume of dextrose equal to what the parenteral nutrition would provide for the 2–4 hours when amphotericin B is infusing in its place. If the source of candidemia is the central venous catheter, it should be removed (Reference 27). Consequently, this will leave the sick preterm neonate with limited peripheral venous access for parenteral nutrition and amphotericin B. The pharmacist should prepare an amphotericin B dose in the same volume and dextrose concentration as the parenteral nutrition, being mindful of the maximal recommended amphotericin B concentration for peripheral administration of 0.1 mg/mL. If the neonate has more than one peripheral intravenous catheter available and can tolerate the 10 mL/kg that an amphotericin B dose represents (1 mg/kg × 0.1 mg/mL), then the least complicated approach is to prepare a 0.1-mg/mL concentration in D_5W (dextrose 5%) for administration in a separate site from the parenteral nutrition.

Other agents used to treat *Candida* LOS are fluconazole, flucytosine, and the echinocandins (Table 6 and Table 7). Fluconazole is not recommended for the empiric therapy of LOS because some non-albicans *Candida* spp. are intrinsically resistant to or have high rates of resistance to fluconazole. If the isolated species is sensitive to fluconazole, it may be used in lieu of amphotericin B to complete the course of therapy. Fluconazole is compatible with parenteral nutrition and hence is much less complicated to administer than

amphotericin B. Oral flucytosine is commonly combined with amphotericin B when CNS infection is present. Caspofungin, micafungin, and anidulafungin all have pharmacokinetic and safety data to guide dosing and monitoring in neonates (References 87–90). These data are preliminary, and more research is needed to determine the optimal dose, better appreciate the potential adverse effects, and develop practical methods of dose preparation and administration for neonates. Clinical experience with the echinocandins in the NICU is also very limited, typically involving cases of persistent fungemia or focal fungal infection and given in combination with amphotericin B. Currently, the echinocandins should only be used under the direction of a pediatric infectious disease consultation for rare cases in which conventional therapy is inadequate.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is an intestinal disease predominantly in very premature neonates older than 7 days. The pathophysiology of NEC is not entirely understood, but it is thought that immature preterm mucosal tissue in the intestinal lumen becomes injured during early postnatal life. Injury can be the result of hypoperfusion and hypoxemia secondary to the typical comorbidities associated with prematurity such as sepsis, low cardiac output, and the presence of umbilical catheters. Intestinal bacteria that colonize the neonate may invade the injured mucosa. The injured and inflamed intestinal portion then becomes symptomatic when challenged with enteral feeding initiation and advancement. The initial clinical presentation is often acute feeding intolerance, abdominal distention, and bloody stools. In severe cases, LOS and rapid clinical deterioration occur, sometimes requiring emergency surgical intervention. Diagnosis is confirmed with a radiographic examination of the abdomen, which reveals evidence of air in the intestinal lining, outside the intestinal lumen, or in the peritoneum if intestinal perforation has occurred (Reference 91). In the United States, 11% of all VLBW neonates will develop NEC during their hospitalization, with an estimated mortality rate of 15% to 30% (Reference 92). Compared with those without NEC matched for GA, survivors of NEC are at high risk of poor neurodevelopmental outcomes such as vision and hearing impairment, cerebral palsy, and cognitive and motor developmental abnormalities (Reference 93).

Antibiotics are a standard intervention for NEC. The intent of antibiotic therapy is to reduce the organism burden contributing to the intestinal disease and prevent translocation into the bloodstream. No single antibiotic regimen is considered superior. Standard LOS therapy that provides broad coverage for nosocomial pathogens and intestinal flora is appropriate for NEC (e.g., vancomycin plus an AMG or other gram-negative coverage). Treatment should continue for 7–14 days. Adding anaerobic coverage by using clindamycin or metronidazole or by substituting AMG or cefotaxime with piperacillin/tazobactam or meropenem can also be considered, particularly when perforation is suspected or confirmed (References 54, 94).

Intravenous Immune Globulin

Meta-analysis of seven prospective placebo or non–treatment-controlled studies of intravenous immune globulin use in neonates with clinical features of sepsis found a significant relative risk reduction of 55% in deaths in those neonates with positive blood or CSF cultures. However, the overall mortality risk reduction was not observed in all study subjects. Because providers do not know when starting treatment whether a neonate will develop proven sepsis, the routine use of intravenous immune globulin to prevent mortality in neonates with presumed sepsis is not recommended (Reference 95). In addition, a large international prospective study of intravenous immune globulin (500 mg/kg administered every 48 hours for two doses) in predominantly VLBW neonates with suspected or proven sepsis did not find a reduction in mortality, subsequent sepsis, or disability compared with placebo, even in the subset of patients with proven sepsis (Reference 96). The routine administration of intravenous immune globulin to prevent nosocomial infection in VLBW preterm neonates is also not recommended because of marginal reductions in infection rates and no reduction in other preterm morbidities or mortality (Reference 97). Experts consider a single dose of intravenous immune globulin 750 mg/kg reasonable in cases of severe sepsis (e.g., hypotension and marked clinical deterioration) when bacterial infection has been proved or is highly likely and when the ANC is less than 1000 cells/mm^3 (References 98, 99).

Prevention

Group B Streptococcus

The most successful strategy for preventing EOS in the United States has been GBS intrapartum antibiotic prophylaxis (Figure 2). This strategy involves screening pregnant women for the presence of vaginal GBS colonization with a lower vaginal and rectal swab collected at 35–37 weeks' GA as part of routine outpatient prenatal care. The collection may also take place in the hospital before 35 weeks if the mother presents with problems that threaten preterm delivery. If the specimen is positive for GBS, the mother is provided prophylactic intravenous antibiotics during labor. Prophylaxis is

discontinued after delivery. Penicillin 5 million units followed by 2.5–3 million units every 4 hours is the regimen of choice for intrapartum antibiotic prophylaxis (Reference 22).

Preterm premature rupture of membranes (pPROM), defined as the spontaneous rupture of the amniotic sac before 37 weeks' (term) gestation and before the onset of labor, increases the risk of intrauterine infection and preterm birth. When pPROM occurs at younger than 34 weeks' gestation, administering systemic antibiotics to the mother can delay birth by more than 7 days and reduce prematurity-associated morbidity in the neonate. Ampicillin or penicillin plus erythromycin or azithromycin decreases the relative risk of confirmed EOS by 39% (Reference 100).

A promising maternal-targeted solution to preventing neonatal sepsis is the development of a GBS vaccine. Ongoing research since the 1990s has contributed to discovering the qualities of a vaccine necessary to elicit a mucosal immune response to the many GBS serotypes known to colonize the maternal genital tract. If ultimately successful, a GBS vaccine administered preconceptionally could prevent GBS-related EOS and LOS. Furthermore, because maternal GBS colonization and urinary tract infection are associated with preterm labor and membrane rupture, a GBS vaccine might prevent pPROM and preterm births and decrease maternal antibiotic use during labor and delivery (References 101, 102).

Herpes Simplex Virus

Cesarean section delivery decreases the incidence of neonatal HSV infection by 80%, compared with vaginal delivery in women with genital HSV lesions or prodromal symptoms that are present at the time of delivery. Oral acyclovir or valacyclovir prophylaxis beginning at 36 weeks' GA in mothers with recurrent genital herpes reduces the recurrence of active maternal HSV infection at delivery by 75% and reduces viral shedding by 90%. The recommended acyclovir dose is 400 mg three times/day or valacyclovir 500 mg twice daily until delivery (Reference 103).

Gonococcal Ophthalmia Neonatorum

Neonatal *Neisseria gonorrhoeae* and *Chlamydia trachomatis* ophthalmic infections are acquired during delivery from exposure to infected maternal cervical secretions. These organisms infrequently can also cause disseminated disease or sepsis (References 104, 105). A single application of erythromycin 0.5% eye ointment to both eyes of newborns within 1 hour of birth is an important intervention for preventing ophthalmic gonococcal infection. Iodine 2.5% solution and tetracycline 1% ointment are also efficacious and used throughout the world. No ocular agent, including erythromycin ointment, is known to be effective at preventing newborn *C. trachomatis* ophthalmic infection (References 104, 106).

Late-Onset Sepsis

Interventions to prevent late-onset infections and sepsis in the NICU include systemic fluconazole, oral nystatin, vancomycin central catheter flush, and breast milk feedings. Fluconazole prophylaxis reduces *Candida* colonization and disseminated infection in at-risk preterm neonates (e.g., birth weight less than 1000 g, 27 weeks or less GA). The dose is 3–6 mg/kg intravenously two or three times/week begun in the first 3 days of life and is continued for 6 weeks or until intravenous access is no longer needed (peripheral or central) (Reference 107). Oral nystatin suspension 100,000 units (1 mL) given by mouth or feeding tube three times/day to VLBW neonates beginning from within the first 3 days and continued until 2 months of life is also effective at preventing invasive fungal infection. The relative reduction in infection rates is about 20% for both fluconazole and nystatin. However, better-quality data are available for fluconazole (References 108, 109). One center that compared fluconazole with nystatin prophylaxis found a higher incidence of mortality from NEC and spontaneous intestinal perforations in preterm neonates who received nystatin (Reference 110).

The early initiation of breast milk feedings instead of cow's milk–based formula reduces the risk of NEC and LOS in preterm neonates (References 111–113). Although breast milk is not a medication, it does have a unique antimicrobial effect. Breast milk contains large quantities of secretory immunoglobulin A (IgA) antibodies that block bacteria from adhering to mucosal membranes and entering tissues (Reference 114). Oligosaccharides in milk also prevent intestinal pathogenic bacteria adhesion and serve as food for desirable intestinal bacteria such as Bifidobacterium (Reference 115). Studies of synthetic "medicinal" oligosaccharide prebiotics and lyophilized powder probiotics such as Bifidobacterium, Lactobacillus, and Saccharomyces as milk additives are encouraging and represent a potential NEC prevention strategy in very preterm neonates (References 116, 117).

Dilute vancomycin 25-mcg/mL flushes administered twice daily through peripherally inserted central venous catheters or administered continuously in parenteral nutrition can prevent CoNS CLABSI in preterm neonates (References 118, 119). Use of the vancomycin flush has been associated with a 6-fold reduction in the incidence of CoNS sepsis compared with placebo (Reference 118). A meta-analysis of vancomycin continuous-infusion studies has identified a 14-fold reduction in CoNS sepsis compared with placebo (Reference

119). Neither of these interventions is recommended for routine use because there is no documented effect on length of stay or mortality. There may also be an increased risk of developing vancomycin-resistant organisms (Reference 120). Nonetheless, their selective use in nurseries with high rates (e.g., greater than 20% of all patients) of staphylococcal CLABSI is considered acceptable (Reference 121).

In addition to recommending appropriate sepsis prevention medications, the pharmacist caring for neonates should participate in multidisciplinary quality assurance activities that prevent sepsis. Examples include implementing medication administration methods that prevent CLABSI and promoting the judicious use of antimicrobials (References 94, 122, 123). Restricting routine gastric acid inhibitor therapy is also encouraged. Stomach acid is an important barrier to infection, and the use of these agents is associated with an increased risk of sepsis, pneumonia, urinary tract infections, and NEC in preterm neonates (References 124, 125).

Conclusions

Sepsis is a significant source of neonatal mortality and long-term morbidity, particularly in VLBW infants. The pharmacist caring for neonates can contribute to improving care by recommending and promptly furnishing individualized appropriate therapy, by closely following the response to therapy, and by helping direct local prescribing practices on the basis of local epidemiology. Because antibiotics are the most common medications used in neonates, pharmacists with a strong working knowledge of sepsis treatment will be a vital asset to the medical team.

Research into the pharmacokinetics and safety of anti-infective agents continues to expand in the United States because of national efforts such as the Pediatric Exclusivity program, the Best Pharmaceuticals for Children Act, and the Pediatric Trials network (see Introduction to Pediatrics chapter). These advances give pharmacists more confidence when making sepsis treatment decisions and contribute to building a larger sepsis treatment armamentarium.

Unfortunately, more or better sepsis treatment choices may not be what neonates need most. Overtreatment of nonseptic neonates remains an unavoidable outcome of a diagnostic dilemma; sepsis is difficult to diagnose because signs and symptoms are nonspecific, and underdiagnosis can lead to disastrous consequences. Any neonate acting abnormally will therefore be treated with anti-infective agents pending the evaluation of maternal history and the results of neonatal physical examination and laboratory testing, all of which suffer from a considerable degree of unreliability and ambiguity. Improvements in the precision of diagnostic tests and sepsis symptom identification, together with treatment improvements, are needed to advance the rational use of antisepsis medications in neonatal care (References 126–128).

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CHAPTER 35

Meningitis in Infants and Children

Erin J. McDade, Pharm.D., BCPS

Learning Objectives

1. Describe the epidemiology and pathophysiology of meningitis.
2. Identify the most common pathogens that cause bacterial and viral meningitis by age group.
3. Describe the signs and symptoms of meningitis in the pediatric population and compare them with those of the adult population.
4. Compare and contrast the diagnostic criteria between bacterial and viral meningitis.
5. Identify appropriate empiric treatment for bacterial meningitis based on the clinical characteristics of a pediatric patient.
6. Develop plan for monitoring pharmacologic therapy for clinical efficacy and potential adverse drug reactions.

Abbreviations in This Chapter

BBB	Blood-brain barrier
CFU	Colony-forming units
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
Hib	*Haemophilus influenzae* type b
HSV	Herpes simplex virus
IDSA	Infectious Diseases Society of America
LP	Lumbar puncture
PCR	Polymerase chain reaction
PCV7	7-valent pneumococcal conjugated vaccine
WBC	White blood cell

Introduction

Meningitis is defined as an inflammation of the meninges and, when suspected, is considered a medical emergency. Meningitis can be caused by a variety of pathogens, including bacteria, viruses, fungi, and parasites. This chapter will focus on bacterial meningitis with a brief overview of viral meningitis. Bacterial meningitis, when untreated, is associated with a mortality rate approaching 100% (Reference 1). With appropriate treatment, the mortality rate decreases to 20% to 30% in neonates and 1% in infants and children (Reference 2). Before vaccinations were used against common bacterial meningitis pathogens such as *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae*, bacterial meningitis occurred in almost 6000 infants and children every year, and 70% of these cases were caused by *H. influenzae* (Reference 3). The introduction of the *H. influenzae* type b (Hib) and 7-valent pneumococcal conjugate (PCV7) vaccines has reduced the incidence of disease caused by these pathogens. In 2000, 13 years after the introduction of the Hib conjugate vaccine, the incidence of meningitis caused by Hib decreased by 99% (Reference 4). Similarly, in 2010, 10 years after the introduction of PCV7, the incidence of invasive pneumococcal disease caused by the seven serotypes contained in the vaccine also decreased by 99% (Reference 5). Because of the emergence of pneumococcal serotypes not covered by the PCV7, *S. pneumoniae* continues to be one of the most prevalent meningitis pathogens. Thus, the FDA approved a 13-valent pneumococcal conjugate vaccine (PCV13) in early 2010 that now covers serotypes 1, 3, 5, 6A, 7F, and 19A in addition to those previously covered by PCV7. It is unclear how the introduction of PCV13 will affect the incidence of pneumococcal meningitis.

Despite reductions in mortality, morbidity associated with bacterial meningitis remains high. In neonates, the risk of neurologic sequelae and disabilities after bacterial meningitis is as high as 56%. Up to 25% of childhood meningitis survivors are at risk of developing major disabilities (References 6, 7). Common meningitis-induced neurologic impairments include behavior and adjustment disorders, hearing or visual loss, intellectual impairment, motor abnormalities, and seizures (Reference 7). Risk factors associated with poor outcomes include young age, delay in presentation, presence of seizures for more than 72 hours, coma, need for inotropes, leukopenia, and pneumococcal etiology (References 6, 8, 9). Fortunately, for meningitis caused by some bacteria, the timely addition of dexamethasone to antibiotic treatment has resulted in a decreased incidence of certain neurologic impairments.

Aseptic meningitis occurs in the absence of bacterial isolation from the cerebrospinal fluid (CSF). Viruses are the most common cause of aseptic meningitis. Viruses can also cause encephalitis, with inflammation that extends beyond the meninges and involves brain parenchyma, often referred to as viral meningoencephalitis. Viral meningitis and meningoencephalitis account for more central nervous system (CNS) infections in the United States than all other pathogens combined

(Reference 10). Despite recent advances in molecular diagnostics, a thorough understanding of viral CNS infections is lacking, which leads to delayed diagnosis and underreporting (Reference 10).

Etiology

Although many pathogens have the potential to cause meningitis, few are responsible for most cases. The most common community-acquired bacterial pathogens depend on the age of the patient; see Table 1 for the most common pathogens based on age group and other predisposing factors.

Bacterial meningitis acquired early in the neonatal period is usually the result of colonization from vaginal delivery. Late-onset neonatal bacterial meningitis and meningitis in all other pediatric age groups are more likely to be caused by a community-acquired pathogen (Reference 12). *Streptococcus agalactiae*, otherwise known as group B *Streptococcus*, is a gram-positive organism commonly found in the vaginal canal and, because of vertical transmission from mother to child, is a common pathogen in neonatal early-onset sepsis and meningitis (see Neonatal Sepsis chapter). *Escherichia coli*, an enteric gram-negative bacillus, is the second leading cause of bacterial meningitis in neonates (Reference 12). Most *E. coli* isolates responsible for meningitis in this age group possess the K1 capsular antigen, which is associated with higher morbidity and mortality rates than other *E. coli* isolates (Reference 13). *Listeria monocytogenes* is a gram-positive bacillus that can be acquired by the mother, most commonly through the consumption of contaminated food, and transmitted vertically to the fetus. *L. monocytogenes*, though not the most common cause of bacterial meningitis in neonates, has the potential to cause more morbidity and mortality than other common pathogens. Because of these risks, empiric coverage of *L. monocytogenes* should always be considered in infants younger than 1 month (Reference 14). Other gram-negative enteric organisms, such as *Klebsiella* spp., can also cause meningitis during the neonatal period.

Bacterial meningitis in patients aged 1–23 months is caused by several different pathogens. The most commonly reported causes in this age group are *S. pneumoniae* and *Neisseria meningitidis*, also known as meningococcal meningitis. *S. agalactiae*, *H. influenzae*, and *E. coli* are also potential pathogens in this age group. As discussed previously, the incidence of *H. influenzae* meningitis decreases dramatically after the introduction of the Hib conjugate vaccine. In fact, the mean age of recorded

Table 1. Common Pathogens by Age Group and Recommended Empiric Therapy for Bacterial Meningitis

Predisposing Factor	Bacteria	Empiric Therapy
Age		
< 1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella* spp.	Ampicillin plus cefotaxime, or ampicillin plus an aminoglycoside
1–23 months	*Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae, Haemophilus influenzae, E. coli*	Vancomycin plus a third-generation cephalosporin
2–18 years	*N. meningitidis, S. pneumoniae*	Vancomycin plus a third-generation cephalosporin
Head Trauma[a]		
Basilar skull fracture	*S. pneumoniae*, *H. influenzae,* group A β-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin
Penetrating trauma	*Staphylococcus aureus*, coagulase-negative staphylococci (especially *Staphylococcus epidermidis*), aerobic gram-negative bacilli (including *Pseudomonas aeruginosa*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Postneurosurgery[a]	Aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus*, coagulase-negative staphylococci (especially *S. epidermidis*)	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
CSF shunt[a]	Coagulase-negative staphylococci (especially *S. epidermidis*), aerobic gram-negative bacilli (including *P. aeruginosa*), *S. aureus*, *Propionibacterium acnes*	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem

CSF = cerebrospinal fluid.

[a]Empiric treatment of pathogens associated with these predisposing factors should be considered in combination with empiric treatment of pathogens based upon age.

Adapted from Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004:39:1267–84, by permission of Oxford University Press (Reference 11).

H. influenzae meningitis increased from 15 months to 25 years of age (Reference 15). Meanwhile, *S. pneumoniae* serotypes not found in PCV7 have increased by 275% and are now the leading cause of meningitis in the 1- to 23-month age group (Reference 16). There are many different strains of *N. meningitidis*, a gram-negative diplococci, but the most common in the United States are serotypes B, C, and Y. Serotype B, which is not covered by the currently licensed meningococcal vaccine, is the most common in infants younger than 1 year (References 17, 18).

N. meningitidis is the most common bacterial pathogen reported in patients between 2 and 18 years of age (Reference 15). The most common meningococcal serotypes in children 11 years and older are C, Y, and W-135 (References 17, 18). The quadrivalent meningococcal vaccine licensed for use in the United States that includes serotypes A, C, Y, and W-135 is recommended for all children between 11 and 12 years of age followed by a booster at 16 years of age. In addition, routine meningococcal vaccination is recommended for those 2 years and older with specific disease states/medical conditions that result in reduced immune response (see Pediatric Vaccines chapter) (Reference 19). *S. pneumoniae* is the second leading cause of meningitis in this age group, and similar to younger children, the most common serotypes found in this age group that now cause meningitis are not found in PCV7.

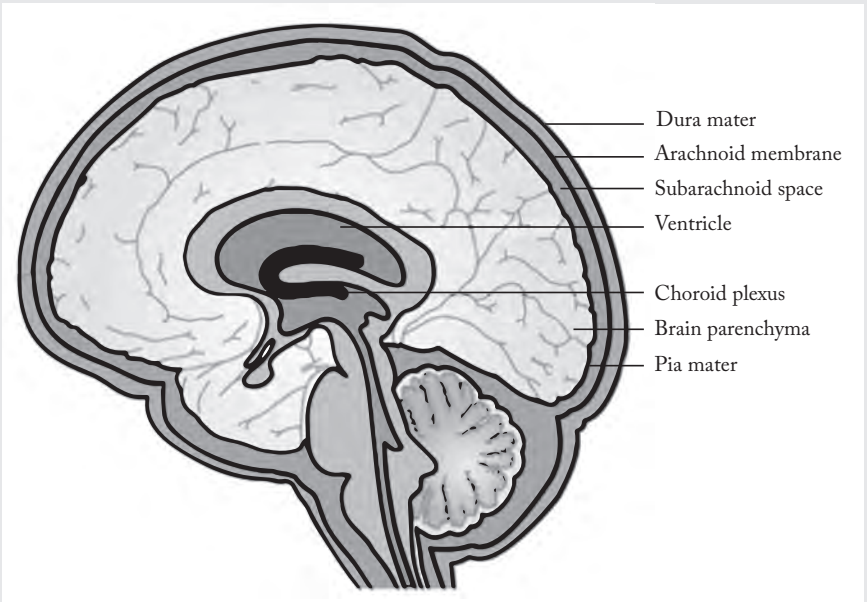


Figure 1. Brain anatomy.

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As discussed previously, viral meningitis and meningoencephalitis account for more cases of meningitis than all other pathogens combined. The most common viral pathogen isolated is the enterovirus, which accounts for more than one-half of all cases each year (Reference 20). More than 50 serotypes of enterovirus have been associated with meningitis (Reference 20). In addition, respiratory viruses such as influenzae and adenoviruses, arboviruses such as West Nile virus, and herpes simplex viruses (HSVs) can cause viral meningitis (References 20, 21).

Anatomy and Physiology of the CNS

Meninges and Cerebrospinal Fluid

The CSF suspends the brain within the protective layers of the meninges. The meninges are composed of three layers: the pia mater, arachnoid mater, and dura mater (Reference 23) (Figure 1). Eighty-five percent of the CSF is produced by the choroid plexuses, which are located in the lateral third and fourth ventricles. Cerebrospinal fluid is secreted from the choroid plexus and flows outward into the subarachnoid space. Cerebrospinal fluid then circulates around the brain and the spinal cord by bulk flow; complete exchange of CSF occurs every 3–4 hours (Reference 23). Cerebrospinal fluid is normally clear, and in infants, children, and adults, it contains less than 50 mg/dL of protein (less than 170 mg/dL in neonates) (References 24, 25). A CSF glucose concentration of 50% to 55% of the peripheral serum concentration (75% to 80% in neonates) is a normal finding in the CSF of infants and children without CNS disease. In addition, in children it is normal for CSF to contain less than 5 white blood cells (WBCs) per cubic millimeter (less than 20 WBCs in neonates) (References 26, 27). These values change in the presence of infection with bacteria or viruses as shown in Table 2.

Blood-Brain Barrier

The interface between the brain and the bloodstream, although commonly referred to as the blood-brain barrier (BBB), consists of two components: the BBB and the blood-CSF barrier. For this chapter, the combination of the BBB and blood-CSF barrier will be referred to as the BBB. The BBB is a functional barrier composed of brain microvascular

Table 2. CSF Findings in Bacterial and Viral Meningitis (References 24–28)

CSF Finding	Normal	Bacterial Meningitis	Viral Meningitis
Opening pressure ($mm\ H_2O$)	50–80	100–300	80–150
Glucose (ratio of CSF to serum)	Neonates: 0.75–0.8 All other ages: 0.5–0.55	Neonates: ≤ 0.6 All other ages: ≤ 0.4	Normal[a]
Protein (mg/dL)	Neonates: < 170 All other ages: < 50	100–500	30–150
WBC ($cells/mm^3$)	Neonates: 0–25 Infants: 0–8 Children and adults: 0–5	1000–5000	100–1000[b]
Differential (%)	> 90 monocytes	80–95 neutrophils	50 lymphocytes[c]

[a]Lower-than-normal glucose has been observed in some patients.
[b]High red blood cell count can be markedly raised in patients with HSV meningoencephalitis.
[c]Initial CSF may reveal a predominance of neutrophils.
CSF = cerebrospinal fluid; HSV = herpes simplex virus; WBC = white blood cell.
Adapted from References 24–28.

endothelial cells that regulate the passage of molecules to and from the brain and protect the brain from microbes and toxins (Reference 29). Tight junctions, the main functional component of the BBB, exist between the brain microvascular endothelial cells and restrict the passage of virtually all molecules. Because of the makeup of the BBB, molecules that are small and lipophilic are more likely to cross the BBB and enter the brain. The presence of transport proteins in the endothelial cells allow the transfer of essential nutrients and molecules to the brain that might not otherwise pass through the tight junctions (Reference 30). During bacterial meningitis, bacteria cause the release of proinflammatory cytokines and toxic compounds, resulting in pleocytosis, increased WBCs in the CSF, and increased permeability of the BBB (Reference 29).

Pathogenesis

Most cases of meningitis occur spontaneously. Although the exact mechanism of CNS invasion is unknown, many cases begin with nasopharyngeal colonization (Reference 31). After mucosal colonization of the nasopharynx, bacteria must overcome the host defense mechanisms to invade the bloodstream and penetrate the CNS, thereby eliciting meningitis and neuronal damage (Figure 2) (Reference 29).

Bacterial colonization of the nasopharyngeal mucosa and systemic invasion are more likely when the bacteria possess fimbriae or a polysaccharide capsule. Fimbriae are organelles found on the surface of many bacterial cells that enhance the adhesion to host cells (Reference 31). *Neisseria meningitidis* is one species known to possess fimbriae. It has been found that 80% of the *N. meningitidis* isolates in the nasopharyngeal mucosa and CSF of patients with meningitis are fimbriated (Reference 32). By inhibiting neutrophil phagocytosis and resisting complement-mediated bactericidal activity, bacterial polysaccharide capsules promote systemic invasion; *H. influenzae, S. pneumoniae*, *N. meningitidis*, and *S. agalactiae*, the most common meningeal pathogens, are examples of encapsulated bacteria. Before the routine use of the Hib vaccine, all strains of encapsulated *H. influenzae* accounted for only 5% of nasopharyngeal isolates; however, more than 95% of meningeal and systemic infections were caused by type b strains (References 31, 33).

The mechanism of meningeal invasion has not been well elucidated; one theory is that a high concentration of bacteria in the bloodstream for a sustained period (at least 6 hours in animal models) increases the likelihood of bacterial penetration into the CNS (Reference 34). Other studies evaluating *E. coli,* Hib, and *S. pneumoniae* in neonates and children show an increased likelihood of developing meningitis with high bacterial blood counts (greater than 100–1000 colony-forming units [CFU]/mL) (References 35–37). The site at which bacteria cross the BBB is also debated. Studies of infant rats and primates have shown that the choroid plexus, the site of the blood-CSF barrier, is the entry site because of its high blood flow rate compared with other areas, although other evidence points toward the dural venous sinus system as the point of entry (Reference 31). To further support the choroid plexus theory, studies have shown that meningeal pathogen receptors are present on choroid plexus cells, facilitating the

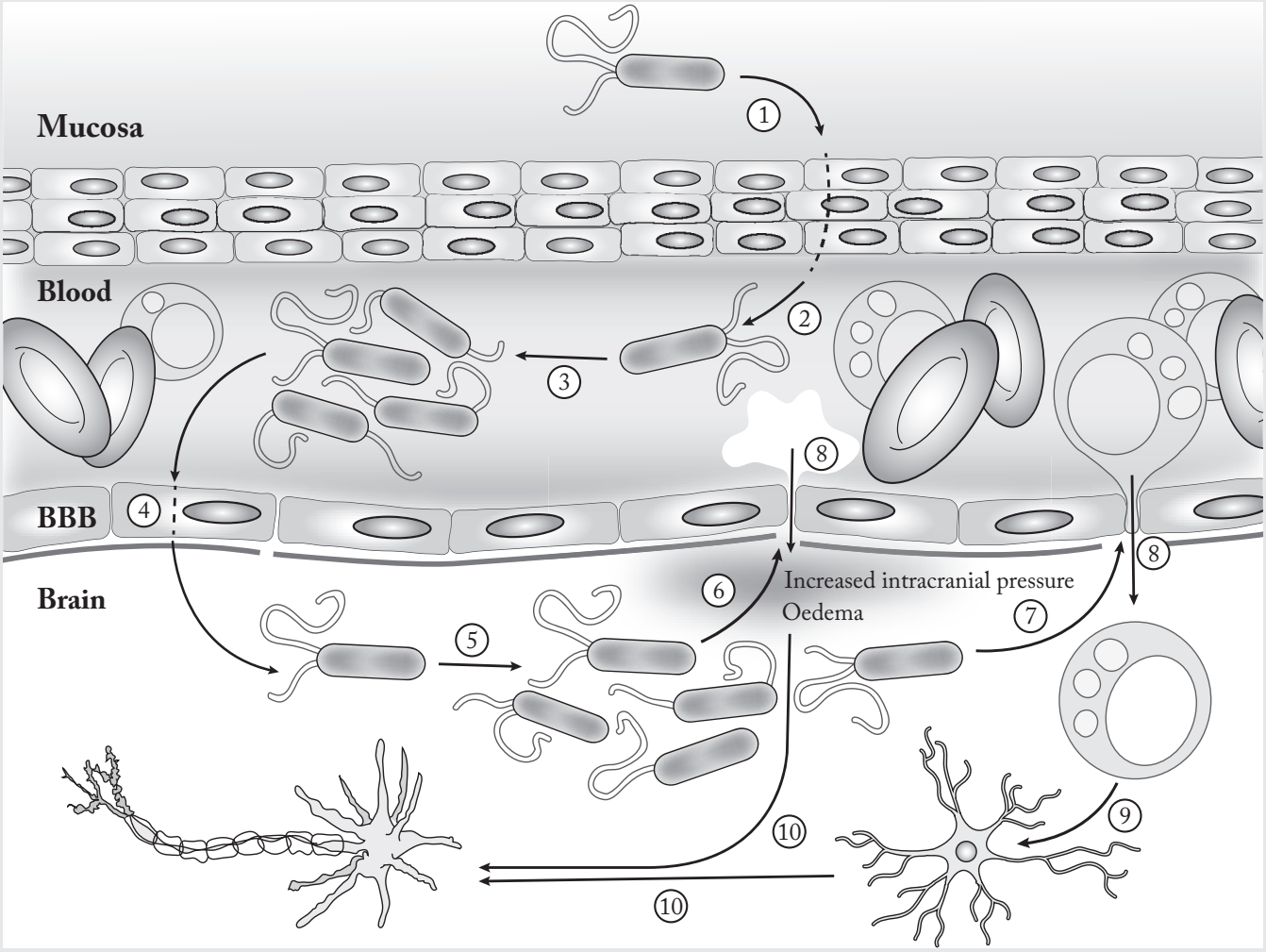


Figure 2. Steps of bacterial host interaction in the pathogenesis of bacterial meningitis.

(1) Mucosal colonization; (2) Invasion of bloodstream; (3) survival and multiplication causing high levels of bacteremia; (4) crossing of the blood-brain barrier (BBB); (5) invasion of the meninges and the central nervous system; (6) bacteria inducing increased permeability of the BBB; (7) pleocytosis; (8) edema and increased intracranial pressure; (9) release of proinflammatory compounds from infiltrated white blood cells and other host cells; (10) neuronal injury.

BBB = blood-brain barrier.

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passage of pathogens across the blood-CSF barrier and into the subarachnoid space (Reference 31). Another hypothesis is that bacteria gain access to the CNS in association with monocytes migrating along normal pathways (Reference 38).

Once in the CNS, host defense mechanisms are usually unable to prohibit bacterial survival and replication, resulting in concentrations as high as 10^7 CFU/mL (Reference 39). The presence of bacteria in the CNS signals the release of proinflammatory cytokines and reactive oxygen species, which promote the migration of WBCs across the BBB. In turn, inflammation weakens the tight junctions of the BBB, allowing easier entry of bacteria and other substances from the bloodstream into the CNS (Reference 29). Bacterial replication, cytokine production, and inflammation continue until appropriate antibiotic therapy is administered. The cycle of inflammation that ensues increases the risk of neuronal damage, increased intracranial pressure, decreased cerebral vascular perfusion, thrombus formation, and hydrocephalus. Not only do replicating bacteria in the CNS lead to inflammation and neuronal damage, but the by-products of bacterial lysis caused by antibiotic therapy also result in subarachnoid inflammation, further increasing the risk of neurologic sequelae (References 40, 41).

Risk Factors

As with patients having many other infectious diseases, immunocompromised patients are at increased risk of developing meningitis. In addition, the incidence and severity of meningitis are increased in young children, with the highest incidence occurring in the first year of life (References 42, 43). The incidence remains high until 2 years of age and then drops off dramatically (Reference 44). Other risk factors include asplenia or splenosis, sickle cell disease and other hemoglobinopathies, terminal complement deficiencies, and recent exposure to someone with meningococcal or *H. influenzae* meningitis. Any situation in which there is a direct route for bacteria to enter the CSF (e.g., surgical procedures, penetrating head trauma, neurosurgical procedures, presence of CSF leak, presence of a CSF shunt, cochlear implants) increases the risk of bacterial meningitis. When meningitis occurs under these circumstances, the most common bacteria found are from the environment (*Staphylococcus* spp. and gram-negative organisms such as *Pseudomonas* spp.) (References 44–46). The focus of this chapter is community-acquired meningitis in the nonsurgical, nontrauma patient; therefore, information regarding the treatment of these organisms is limited to Table 1 and Table 3.

Table 3. Recommendations for Specific Therapy Based on Isolated Pathogen and Susceptibility

Microorganism, Susceptibility	Standard Therapy	Alternative Therapies
Streptococcus agalactiae	Penicillin G or ampicillin	Third-generation cephalosporin[a]
Escherichia coli and *Klebsiella* spp.	Third-generation cephalosporin	Aztreonam, fluoroquinolone, meropenem, trimethoprim/sulfamethoxazole,[b] ampicillin
Listeria monocytogenes	Penicillin G or ampicillin	Meropenem
Streptococcus pneumoniae Penicillin MIC		
< 0.1 mcg/mL	Penicillin G or ampicillin	Third-generation cephalosporin[a]
0.1–1 mcg/mL[c]	Third-generation cephalosporin[a]	Cefepime, meropenem
≥ 2 mcg/mL	Vancomycin plus third-generation cephalosporin[a]	Fluoroquinolone[d]
Cefotaxime/ceftriaxone MIC ≥ 1 mcg/mL	Vancomycin plus third-generation cephalosporin[a]	Fluoroquinolone[d]
Haemophilus influenzae		
β-Lactamase negative	Ampicillin	Third-generation cephalosporin,[a] cefepime, fluoroquinolone
β-Lactamase positive	Third-generation cephalosporin[a]	Cefepime, fluoroquinolone
Neisseria meningitidis Penicillin MIC		
< 0.1 mcg/mL	Penicillin G or ampicillin	Third-generation cephalosporin[a]
0.1–1 mcg/mL	Third-generation cephalosporin[a]	Fluoroquinolone, meropenem
Staphylococcus aureus		
Methicillin susceptible	Nafcillin or oxacillin	Vancomycin, meropenem
Methicillin resistant	Vancomycin	Trimethoprim/sulfamethoxazole,[b] linezolid
Staphylococcus epidermidis	Vancomycin	Linezolid
Pseudomonas aeruginosa	Cefepime or ceftazidime	Aztreonam, ciprofloxacin, meropenem

[a]Cefotaxime or ceftriaxone (avoid the use of ceftriaxone in the first 28 days of life).
[b]Avoid the use of trimethoprim/sulfamethoxazole in the first 28 days of life.
[c] Cefotaxime/ceftriaxone-susceptible isolates.
[d] Guidelines recommend gatifloxacin or moxifloxacin, but there are no dosing recommendations for use in pediatric patients.
MIC = minimum inhibitory concentration.
Adapted from Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004:39:1267–84, by permission of Oxford University Press (Reference 11).

Clinical Presentation and Diagnosis

Signs and Symptoms

The signs and symptoms of meningitis in the pediatric population, unlike the adult population, are generally nonspecific and can lead to misdiagnosis, especially in young children. Infants and young children often present with the following signs and symptoms: fever, poor feeding, vomiting, lethargy, apnea, irritability, and seizures (more commonly seen in pediatric patients than in adults). In addition, a bulging fontanel can often be seen in neonates and young infants. A study of 110 pediatric patients with bacterial meningitis found that the most common presenting symptoms were irritability and impaired consciousness in patients 1–5 months and 6–11 months of age, respectively. In children 12 months or older, vomiting and nuchal rigidity (neck stiffness) were the most commonly seen signs and symptoms of meningitis (Reference 47). This supports the premise that older children and adolescents are more likely to present with classic meningeal signs and symptoms of nuchal rigidity headache and photophobia than are infants and young children. In addition, compared with infants and children younger than 18 months, older children and adolescents are more likely to present with a positive Kernig's and/or Brudzinski's sign (Figure 3, Figure 4, and Figure 5) (References 28, 48).

A systematic review reported that a history of bulging fontanel, nuchal rigidity, seizures (if patient is out of the age range for febrile seizures), and poor feeding were associated with an increased likelihood of meningitis. According to the same review, the presence of the following findings on physical examination was

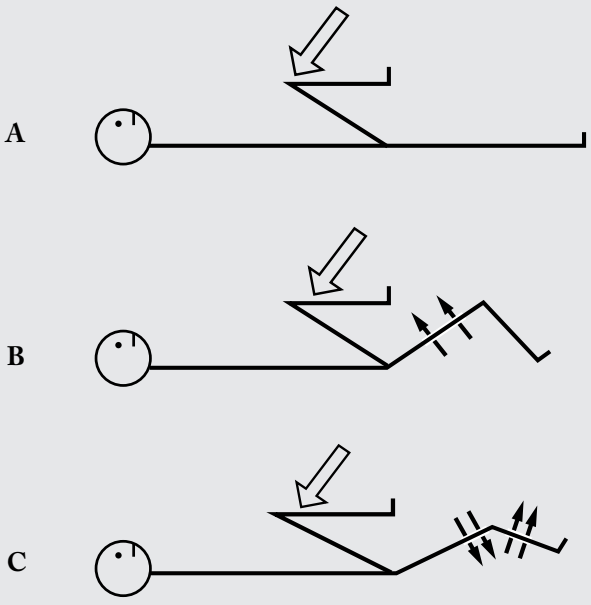


Figure 3. Brudzinski's leg sign.

(A) Examiner passively flexes patient's leg (large arrow). (B) The identical contralateral sign: contralateral leg begins to flex (small arrows). (C) The reciprocal contralateral sign: the same leg that exhibited the active flexion begins to extend spontaneously—a reflex resembling a little kick (double arrows).

Verghese A, Gallemore G. Kernig's and Brudzinski's signs revisited. Rev Infect Dis 1987;9:187–92, by permission of Oxford University Press (Reference 49).

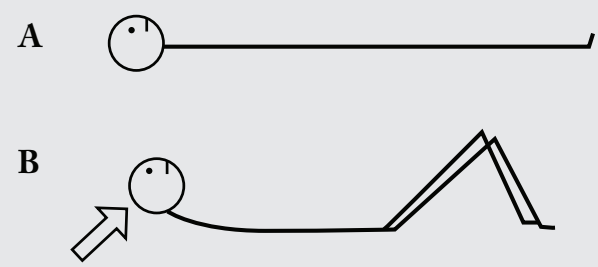


Figure 4. Brudzinski's neck sign.

Flexion of the neck (A) by the examiner produces hip and knee flexion (B).

Verghese A, Gallemore G. Kernig's and Brudzinski's signs revisited. Rev Infect Dis 1987;9:187–92, by permission of Oxford University Press (Reference 49).

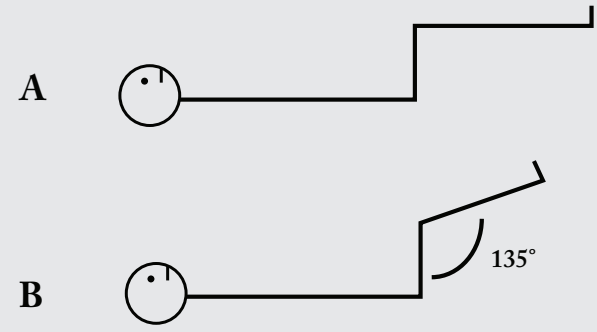


Figure 5. Kernig's sign.

Flexion of the knees to 90 degrees (A), the examiner attempts to extend the knees. Once the patient's knee angle reaches about 135 degrees (B), the examiner cannot extend any further because of contracture or extensor spasm.

Adapted from Verghese A, Gallemore G. Kernig's and Brudzinski's signs revisited. Rev Infect Dis 1987;9:187–92, by permission of Oxford University Press (Reference 49).

also associated with increased likelihood of meningitis: jaundice, bulging fontanel, toxic appearance, positive Kernig's and/or positive Brudzinski's sign, and increased tone (Reference 50).

Diagnosis

Although most diagnostic signs and symptoms of meningitis can be debated, it is well known that many are nonspecific and that diagnosis can be easily missed, resulting in greater morbidity and mortality. A definitive diagnosis of meningitis can only be made through an examination of the CSF; therefore, in most cases, a lumbar puncture (LP) is required. After the removal of CSF by LP, it is normal to have mild, transient lowering of the CSF pressure (Reference 11). In some patients with certain intracranial lesions, this decrease in CSF pressure could precipitate brain herniation. Given that the risk of herniation is restricted to certain patient populations and the time required for neuroimaging can delay treatment with antibiotics, computed tomography (CT) scans should not be performed routinely (Reference 51). The Infectious Diseases Society of America (IDSA) recommends that only infants and children with certain signs and symptoms receive a head CT scan before an LP (Figure 6) (Reference 11).

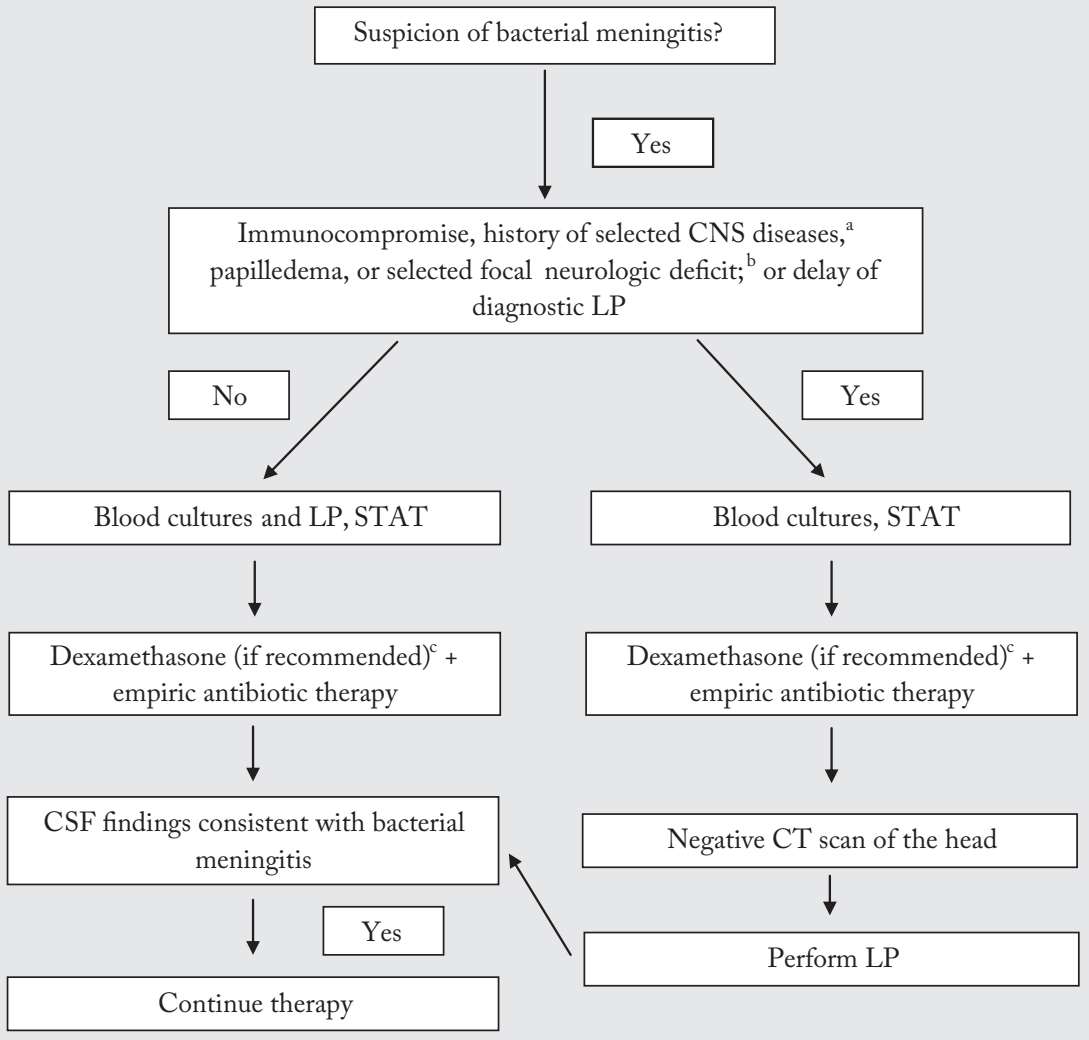


Figure 6. Decision tree for diagnosis and treatment of suspected meningitis.

[a]Includes diseases associated with CSF shunts, hydrocephalus, or trauma; diseases occurring after neurosurgery; or space-occupying lesions.
[b]Palsy of cranial nerves VI or VII is not an indication to delay LP.
[c]See text for adjunctive dexamethasone recommendations.
CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; LP = lumbar puncture.
Adapted from Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004:39:1267–84, by permission of Oxford University Press (Reference 11).

Once an LP has been performed, CSF should be sent to the laboratory for cell counts (WBC and RBC), glucose and protein content, and Gram stain and culture. In addition, measuring the opening CSF pressure during LP may provide diagnostic information. Table 2 summarizes the CSF findings in patients with bacterial and viral meningitis. While CSF RBC count is not used for direct diagnosis of meningitis, it is routinely used to determine occurrence of a traumatic LP or presence of subarachnoid or intracerebral hemorrhage. If RBCs are present in the CSF, the WBC count could be falsely elevated because of WBCs introduced from the bloodstream. Performing a Gram stain on the CSF allows an accurate identification of the causative organism in most community-acquired bacterial meningitis cases with a specificity of 97% (Reference 52). The accuracy by which a Gram stain detects a bacterial pathogen is directly related to the concentration of bacteria in the CSF: the higher the concentration, the greater the chance of pathogen detection (Reference 53). In addition, it is exceedingly important to note whether the patient received antibiotic therapy before LP. Sterilization of the CSF can occur after one dose of intravenous antibiotic therapy. The speed at which the CSF will become sterile depends on the bacterial pathogen present and the antibiotic used (Reference 54).

Other laboratory tests that may help determine the presence of bacterial meningitis include latex agglutination, limulus lysate assay, and polymerase chain reaction (PCR). Latex agglutination is a rapid test that uses either a serum containing bacterial antibodies or commercially available antisera that are directed against the capsular polysaccharides of meningeal pathogens (Reference 11). A rapid turnaround time, simple technique, and low cost are advantages to the use of latex agglutination. The sensitivity of the test depends on the meningeal pathogen that is present and the specific latex agglutination test. Depending on the assay used, average sensitivities range from 82% to 94% for Hib, 81% to 100% for *S. Pneumoniae*, 73% to 100% for *Streptococcus* group B, and 55% to 74% for *N. meningitidis* (Reference 27). Although this test may be useful to determine the pathogen present, it does not appear to alter the decision to administer antimicrobial therapy. Therefore, the IDSA does not recommend the routine use of latex agglutination to rapidly determine bacterial etiology. The guidelines recommend the use of this modality in patients who have been pretreated with antibiotic therapy and whose CSF Gram stain and culture results are negative (Reference 11).

The limulus lysate assay, which is prepared from an amebocyte of the horseshoe crab, is designed as a test to determine the presence of gram-negative meningitis. The test works by giving a positive result in the presence of endotoxin from gram-negative bacteria. The sensitivity of this test is controversial, with some evidence to support that it is not sensitive enough to serve as a screening tool in the diagnosis of neonates with gram-negative meningitis (Reference 55). Therefore, the IDSA does not recommend the routine use of the limulus lysate assay for patients with meningitis (Reference 11).

Polymerase chain reaction is a primer-mediated technique for the enzymatic amplification of specific DNA sequences. It can be used to detect the presence of many pathogens, including the most common causes of bacterial meningitis (*N. meningitidis*, *S. pneumoniae*, Hib, *S. agalactiae*, and *L. monocytogenes*). The sensitivity and specificity of PCR vary depending on the test, but when a broad range of bacterial primers are used, the sensitivity is 100% with a specificity of 98%, a positive predictive value of 98%, and a negative predictive value of 100% (Reference 56). The IDSA guidelines suggest PCR is useful for excluding the diagnosis of bacterial meningitis and that it potentially plays an influential role in the decision to initiate or discontinue antibiotic therapy (Reference 11).

Clinicians are often faced with the diagnostic dilemma of differentiating between bacterial and viral meningitis, especially when CSF Gram stain and culture yield negative results. Several tests have been shown to be somewhat helpful in differentiating bacterial from viral meningitis, including CSF lactate concentration, serum C-reactive protein concentration, and serum procalcitonin. Although these tests have not yet replaced standard measures for the diagnosis of bacterial versus viral meningitis, high CSF lactate concentrations, high serum C-reactive protein, and serum procalcitonin greater than 2 ng/mL have been found to be indicators of bacterial rather than viral meningitis (References 57–59). In addition, the presence of a CSF glucose concentration of less than 34 mg/dL, a ratio of CSF to serum glucose of less than 0.23, a CSF protein concentration of greater than 220 mg/dL, a CSF leukocyte count of more than 2000 leukocytes/mm^3, or a CSF neutrophil count of greater than 1180 neutrophils/mm^3 is an individual predictor of bacterial, rather than viral, meningitis with 99% or higher certainty (References 60, 61).

The diagnosis of viral meningitis, in most clinical settings, involves the exclusion of bacterial meningitis. In addition to CSF cell counts, glucose and protein concentrations, and viral culture, PCR has become an important diagnostic tool to determine the cause of meningitis. Commercial PCR kits are available for the detection of various HSVs as well as enteroviruses (References 62–64).

Treatment

Empiric therapy for the treatment of community-acquired bacterial meningitis depends on the age of the patient and should cover all commonly encountered organisms for that age group (Table 1). Once cultures and sensitivities are reported, the antimicrobial therapy

should be narrowed for treatment of the specific isolated organism (Table 3). For maximum penetration into the CSF, antibiotics should be administered intravenously; recommended antimicrobial doses are summarized in Table 4. The duration of antibiotic therapy depends on the offending pathogen. The IDSA recommends a 7-day treatment course for meningitis caused by *N. meningitidis* and *H. influenzae*, a 10- to 14-day course for *S. pneumoniae* meningitis, a 14- to 21-day course for *S. agalactiae* meningitis, 21 days for *E. coli* (and other aerobic gram-negative bacilli), and 21 days or more for *L. monocytogenes* meningitis (Reference 11). In addition, guidelines recommend that neonates with gram-negative meningitis be treated for 2 weeks after the first sterile CSF culture or for 3 weeks or more, whichever is longer (Reference 11). The remainder of this section focuses on the treatment of specific community-acquired bacteria, adjunctive treatment, and supportive care.

S. agalactiae (Group B Streptococci)

S. agalactiae is susceptible to various antibiotics, but with a goal of achieving adequate CNS penetration with a narrow-spectrum agent, treatment with penicillin, ampicillin, or a cephalosporin is recommended. Ampicillin is typically the drug of choice for empiric coverage of *S. agalactiae*. Once *S. agalactiae* has been identified and clinical and microbiologic response has been documented, penicillin or ampicillin alone can be used. To minimize the potential development of antibiotic resistance, penicillin should be used, if possible, because of its narrow spectrum of activity (References 12, 67). Although higher-than-normal doses of antibiotics are routinely used in the treatment of meningitis because it is a sequestered infection site, use of these high doses is even more important with *S. agalactiae* meningitis in neonates. Neonates often present with a higher CSF bacterial load than older age groups, and *S. agalactiae* has a minimum bactericidal concentration that is 10-fold higher than other *Streptococcus* spp., warranting more aggressive doses of antibiotics than in infants and children (Reference 64).

E. coli and *Klebsiella* spp.

Although the combination of ampicillin and an aminoglycoside is adequate for most empiric treatments of *E. coli* and *Klebsiella* infections in neonates, emerging ampicillin resistance, coupled with the relatively poor CSF penetration of aminoglycosides, warrants the use of a different agent. The most commonly used antibiotic in this setting is cefotaxime, a third-generation cephalosporin. Although second- and third-generation cephalosporins have similar spectra of activity against common meningeal pathogens, the use of third-generation cephalosporins for the treatment of meningitis has been shown to result in better outcomes (Reference 68). For several reasons, cefotaxime is preferred to other intravenous third-generation cephalosporins such as ceftazidime and ceftriaxone. Ceftazidime provides unnecessarily broad gram-negative coverage for community-acquired meningitis, including *Pseudomonas aeruginosa*, and less gram-positive activity than cefotaxime. Unlike cefotaxime, ceftriaxone is up to 95% protein bound and has the ability to displace bilirubin from albumin-binding sites. In neonates, increased free bilirubin increases the risk of kernicterus, a neurologically devastating condition in which bilirubin deposits in the basal ganglia of the brain; therefore, cefotaxime is preferred in this population. Although cefotaxime has a broader spectrum of activity than aminoglycosides, which may lead to an increased incidence of antibiotic resistance, it safely reaches much higher CSF concentrations than aminoglycosides. Cefotaxime may decrease the risk of prolonged infection and treatment failure, so it should be considered for empiric coverage of suspected neonatal meningitis caused by *E. coli* and *Klebsiella* spp. (Reference 12).

L. monocytogenes

As discussed previously, *L. monocytogenes* is a potentially devastating meningeal pathogen in neonates. The mainstay of treatment for *L. monocytogenes* is the combination of ampicillin and gentamicin. Although ampicillin is typically the drug of choice for treatment, the combination of ampicillin and an aminoglycoside is typically used initially because of improved survival observed in animal models (References 14, 69). Gentamicin is the preferred aminoglycoside because tobramycin and amikacin are typically reserved for resistant organisms.

S. pneumoniae

S. pneumoniae is the most common and second most common pathogen in patients 1–23 months and 2–18 years of age, respectively. Historically *S. pneumoniae* was best treated by penicillin. In the 1960s, the first case of penicillin-resistant *S. pneumoniae* was documented, and since then, the emergence of resistant pneumococcus has increased around the world. More recently, pneumococcal isolates resistant to third-generation cephalosporins have become more common (References 15, 70). In 1998, data published from the Active Bacterial Core Surveillance program in the United States showed that as many as 35% of invasive *S. pneumoniae* isolates were resistant to penicillin, and 14% of isolates were resistant to cefotaxime (Reference 71). For this reason, vancomycin should always be given with a third-generation cephalosporin, either ceftriaxone or cefotaxime, for empiric treatment of suspected meningitis in patients 1 month and older for adequate coverage of *S. pneumoniae*

Table 4. Antimicrobial Dosing for Meningitis (References 11, 24, 45, 65, 66)

Antimicrobial Agent	CSF Penetration[a]	Dose (mg/kg/dose), dosing interval (hours)			Maximum Single Dose *(unless stated otherwise)*	Comments
		Neonates, age in days (> 2000 g)		Infants and Children		
		0–7	8–28			
Amikacin	-	10 mg/kg, every 12	10 mg/kg, every 8	10 mg/kg, every 8	N/A[b, c]	Goal peak: 30–40 mcg/mL Goal trough: < 10 mcg/mL
Ampicillin	+	100 mg/kg, every 8	75 mg/kg, every 6	75 mg/kg, every 6	2000 mg	
Aztreonam	+	30 mg/kg, every 8	30 mg/kg, every 6	30 mg/kg, every 6	2000 mg	
Cefepime	+	50 mg/kg, every 12	50 mg/kg, every 12	50 mg/kg, every 8	2000 mg	
Cefotaxime	+	50 mg/kg, every 8–12	50 mg/kg, every 6–8	75 mg/kg, every 6	2000 mg	
Ceftazidime	+	50 mg/kg, every 8–12	50 mg/kg, every 8	50 mg/kg, every 8	2000 mg	
Ceftriaxone	+	—	—	50 mg/kg, every 12	2000 mg	Not for neonates.[d] Avoid use with calcium-containing IV fluids.[e]
Chloramphenicol	++	—	—	25 mg/kg, every 6	4000 mg/day	Not routinely used because of adverse effects.
Ciprofloxacin	+	—	—	10–15 mg/kg, every 12	800 mg/day	Not first line in pediatrics[f]
Gentamicin	-	2.5 mg/kg, every 12	2.5 mg/kg, every 8	2.5 mg/kg, every 8	N/A[b, c]	Goal peak: 8–10 mcg/mL Goal trough: < 2 mcg/mL
Meropenem	+	20 mg/kg, every 12	20 mg/kg, every 8	40 mg/kg, every 8	2000 mg	
Nafcillin	+	25 mg/kg, every 8	25–35 mg/kg, every 6	50 mg/kg, every 6	12 g/day	
Oxacillin	+	50 mg/kg, every 8	50 mg/kg, every 6	50 mg/kg, every 6	12 g/day	
Penicillin G	+	50,000 units/kg, every 8	50,000 units/kg, every 6	66,000 units/kg, every 4	24 million units/day	
Rifampin	++	—	10 mg/kg, every 12	10 mg/kg, every 12	600 mg	
Tobramycin	-	2.5 mg/kg, every 12	2.5 mg/kg, every 8	2.5 mg/kg TMP, every 8	N/A[b, c]	Goal peak: 8–10 mcg/mL Goal trough: < 2 mcg/mL
Trimethoprim/ sulfamethoxazole	++	—	—	5 mg/kg TMP, every 6–8	N/A[b]	Not for use in neonates[d]
Vancomycin	+	15 mg/kg, every 8–12	15 mg/kg, every 6–8	15 mg/kg, every 6	N/A[b, c]	Goal trough: 15–20 mcg/mL[g]

[a]++: Therapeutic levels in the CSF with or without inflammation of the meninges; +: therapeutic levels in the CSF with inflammation of the meninges; -nontherapeutic levels in the CSF without inflammation and minimal penetration with inflammation.
[b]No true maximum dose.
[c]Monitor serum concentrations, doses should be adjusted to achieve appropriate serum concentrations.
[d]Highly protein bound; risk of bilirubin displacement and development of kernicterus.
[e]Because of risk of precipitation.
[f]Reference 66.
[g]Reference 11.
CSF = cerebrospinal fluid; IV = intravenous; N/A = not applicable; TMP = trimethoprim.
Adapted from Tunkel AR, Hartman BJ, Kaplan SL, Kaufman BA, Roos KL, Scheld WM, et al. Practice guidelines for the management of bacterial meningitis. Clin Infect Dis 2004:39:1267–84, by permission of Oxford University Press (Reference 11).

(Reference 11). Of note, the use of ceftriaxone in patients older than 1 month is safe because the risk of kernicterus is greatly decreased after this time. As is true with all other isolated pathogens, if *S. pneumoniae* is isolated, the antibiotic therapy should be tailored to the narrowest agent on the basis of susceptibility.

H. influenzae

Despite the routine use of the Hib conjugate vaccine in the United States, *H. influenzae* remains a potential and important cause of meningitis in infants 1–23 months of age. In the 1970s, β-lactamase–producing *H. influenzae* resulted in penicillin treatment failures. In some areas of the United States, the incidence of β-lactamase–positive *H. influenzae* is now approaching 50% (Reference 70). To overcome this resistance and reduce the risk of treatment failures, a third-generation cephalosporin, either cefotaxime or ceftriaxone, is recommended for empiric treatment of patients 1–23 months of age who are at risk of *H. influenzae* meningitis (Reference 11). If *H. influenzae* is isolated from the CSF and the β-lactamase enzyme is not present, antibiotic therapy should be narrowed on the basis of susceptibilities.

N. meningitidis

Penicillin is the treatment of choice for *N. meningitidis*, the most common meningeal pathogen isolated in patients older than 2 years. Although penicillin-resistant strains of *N. meningitidis* are rare, a third-generation cephalosporin, either ceftriaxone or cefotaxime, should be used empirically until susceptibilities are reported. If a penicillin-susceptible strain of *N. meningitidis* is isolated, therapy should be changed to penicillin for the duration of treatment. Although *N. meningitidis* is a highly pathogenic organism, it is easily treated with appropriate antibiotic therapy. In one study, after the single dose of a third-generation cephalosporin, all CSF cultures were negative after just 2 hours, much less time than was seen for other pathogens (Reference 54). The treatment duration required for meningococcal meningitis is 7 days, much shorter than for other pathogens. In fact, some evidence, although limited, supports even shorter durations with no increased incidence of relapse (Reference 72).

Viral Pathogens

Therapy for viral meningitis pathogens is limited; therefore, supportive care is typically the mainstay of treatment. Unfortunately, no antiviral treatment is available for enterovirus, the most common viral pathogen isolated in viral meningitis cases. If HSV is suspected, especially in neonates, parenteral acyclovir should be initiated and continued for 14–21 days until HSV infection is ruled out, at which point acyclovir can be discontinued. Acyclovir dosing in neonates, infants, and children younger than 12 years with suspected HSV meningitis or encephalitis is 20 mg/kg/dose intravenously administered every 8 hours. Of note, some experts recommend 15 mg/kg/dose every 8 hours for children older than 2 months to younger than 12 years. For children 12 years and older, a dose of 10 mg/kg intravenously administered every 8 hours is recommended (Reference 73). Acyclovir has the potential to cause nephrotoxicity; therefore, pharmacists should ensure patients receive adequate hydration as well as proper monitoring of urine output and renal function, especially when acyclovir is combined with other nephrotoxic agents. There are no effective therapies for the other potential viral causes of meningitis, such as respiratory viruses or arboviruses.

Supportive Care

The maintenance of normal temperature and blood pressure, adequate cerebral perfusion pressure, and management of increased intracranial pressure is paramount in preventing the most life-threatening complications of bacterial meningitis. Strategies used to reduce intracranial pressure include bed head elevation of 30 degrees, avoidance of frequent vigorous procedures, mannitol or hypertonic saline administration, and, potentially, administration of high-dose barbiturates (Reference 45). In addition, patients who become obtunded and unable to protect their airway often require intubation and mechanical ventilation.

Adjunctive Treatment with Dexamethasone

As discussed previously, bacterial meningitis remains an important and significant cause of morbidity and mortality in children. The neurologic sequelae associated with this disease are mainly a result of the inflammatory processes from bacterial proliferation and bacterial lysis in the CSF. For this reason, dexamethasone, a corticosteroid with potent anti-inflammatory effects, has been studied in patients with bacterial meningitis to decrease the incidence of morbidity and mortality. It has been shown that dexamethasone, when used in the appropriate pediatric patient, can improve morbidity but does not seem to affect mortality (References 11, 74, 75).

Dexamethasone use in neonatal meningitis is not well studied; therefore, it is not recommended for treatment of bacterial meningitis in this population. According to a recent meta-analysis, in children older than 1 month with bacterial meningitis mainly caused by *H. influenzae*, administration of dexamethasone decreased the risk of hearing loss (Reference 74). Because of the potential for increased inflammation as a result of bacterial lysis after antibiotic therapy, dexamethasone should be administered before the first dose of

antibiotic therapy to be most effective. The latest IDSA treatment guidelines for meningitis recommend the use of dexamethasone, at a dose of 0.15 mg/kg every 6 hours for 2–4 days, in infants and children with *H. influenzae* meningitis as long as it is initiated before the administration of antibiotic therapy (Reference 11).

The use of adjunctive dexamethasone treatment for pneumococcal meningitis is controversial. Given the lack of supporting evidence, the IDSA guidelines state that dexamethasone therapy should be considered in patients with pneumococcal meningitis and that the potential risks and benefits should be weighed before initiating treatment (References 11, 76). More recently, it was found that in high-income countries, dexamethasone treatment has a protective effect against the development of hearing loss in non–*H. influenzae* meningitis in children (Reference 74). There is no evidence supporting the use of adjunctive dexamethasone in meningococcal or gram-negative meningitis.

Adjunctive Treatment with Rifampin

Rifampin is an agent commonly used synergistically in combination with other antibiotics for the treatment of *Staphylococcus* spp. Although rifampin may be an attractive agent for the treatment of CNS infections because of its excellent BBB penetration, resistance to rifampin develops quickly when it is used alone. Therefore, rifampin should always be used in combination with another agent when treating bacterial meningitis. On the basis of its activity against *Staphylococcus* spp., it is recommended that rifampin be considered in addition to vancomycin in patients with CNS shunt infections, particularly if the shunt is not going to be removed (Reference 11). Although data are limited, some experts recommend the addition of rifampin to either cefotaxime or ceftriaxone for the treatment of *S. pneumoniae* meningitis in the following circumstances: the patient's condition continues to deteriorate after 24–48 hours of therapy, a repeat CSF culture shows continued growth or does not show a significant reduction in the number of organisms growing, or the *S. pneumoniae* isolate has a cefotaxime/ceftriaxone MIC greater than 2 mcg/mL (References 11, 77).

Monitoring Treatment

Patients should be monitored for improvement in signs and symptoms of meningitis. For patients who respond appropriately to treatment, repeat LP is not routinely recommended. For patients in whom symptoms do not improve after 48 hours of therapy, repeat LP should be considered (Reference 11). This is especially true for patients with pneumococcal meningitis that is resistant to penicillin or cephalosporins, neonates with meningitis caused by gram-negative bacteria, or those who have received adjunctive dexamethasone therapy. Patients should also be monitored for adverse effects of antibiotic/antiviral treatment (Table 5).

Table 5. Common Adverse Effects of Therapy (Reference 65)

Agent	Adverse Effects
Acyclovir	Rash, nausea, phlebitis, nephrotoxicity, elevated liver function tests
Aminoglycosides (amikacin, gentamicin, tobramycin)	Nephrotoxicity, ototoxicity
Aztreonam	Neutropenia, elevated liver function tests, pain at injection site, elevated serum creatinine
Cephalosporins (ceftriaxone, cefotaxime, ceftazidime, cefepime)	Hypersensitivity reactions, nausea, vomiting, diarrhea, pain at injection site, biliary sludging (ceftriaxone)
Chloramphenicol	Gray baby syndrome, reversible bone marrow suppression, aplastic anemia
Ciprofloxacin	Neurologic events (dizziness, nervousness), rash, photosensitivity, nausea, vomiting, tendon rupture
Meropenem	Hypersensitivity reactions, headache, rash, nausea, vomiting, diarrhea, phlebitis, seizures (rare)
Penicillins (ampicillin, nafcillin, oxacillin, penicillin G)	Hypersensitivity reactions, seizures (with high concentrations), bone marrow suppression, elevated liver function tests, interstitial nephritis (rare)
Trimethoprim/sulfamethoxazole	Nausea, vomiting, rash, jaundice/kernicterus in neonates, blood dyscrasias (rare), hepatotoxicity (rare)
Vancomycin	Red man syndrome, nephrotoxicity, hypotension, fever, neutropenia

Table 6. Chemoprophylaxis Agents and Dosing (References 78, 79)

Meningeal Pathogen	Rifampin[a]	Ceftriaxone	Ciprofloxacin[a, b]
Haemophilus influenzae type b	< 1 month old: 10 mg/kg orally every day for 4 days ≥ 1 month old: 20 mg/kg (maximum 600 mg) orally every day for 4 days	Not recommended	Not recommended
Neisseria meningitidis	< 1 month old: 5 mg/kg orally every 12 hours for 2 days ≥ 1 month old: 10 mg/kg (maximum 600 mg) orally every 12 hours for 2 days	< 15 years old: 125 mg intramuscularly once ≥ 15 years old: 250 mg intramuscularly once	≥ 1 month old: 20 mg/kg (maximum 500 mg) orally once

[a]Not recommended for use in pregnant women.
[b]Use only if fluoroquinolone-resistant strains of *N. meningitidis* have not been identified in the community.

Chemoprophylaxis

Chemoprophylaxis for *H. influenzae* should be provided for specific household contacts. Household contact is defined as people residing with the index patient or nonresidents who spent 4 or more hours with the index patient for at least 5 of the last 7 days preceding the day of hospital admission. Any household with at least one child who is younger than 4 years and unimmunized or incompletely immunized, or any household with a person who is immunosuppressed (regardless of immunization status), should also receive chemoprophylaxis. Chemoprophylaxis is also recommended for nursery school and day care center contacts when two or more *H. influenzae* cases have occurred in the past 60 days (Reference 78).

Chemoprophylaxis is recommended in the following situations if a documented case of meningococcal meningitis occurs: household contact (as previously defined), especially children younger than 2 years; day care or preschool contact at any time during the previous 7 days from the onset of illness; anyone who has had direct exposure to the index patient's secretions through kissing, sharing toothbrushes, or eating utensils; and markers of close social contact at any time during the previous 7 days leading up to illness. In addition, people who have frequently slept in the same dwelling as the index patient during the 7 days preceding the illness or any passenger seated directly next to the index case during airline flights lasting more than 8 hours during the 7 days before illness should receive chemoprophylaxis for meningococcal disease. Only health care providers who have provided mouth-to-mouth resuscitation or had unprotected contact during endotracheal intubation at any time within 7 days before the onset of illness should receive chemoprophylaxis. Otherwise, routine chemoprophylaxis for health care providers is not recommended (Reference 79). See Table 6 for a list of recommended chemoprophylaxis agents and dosage.

Vaccination

Vaccination is the most effective way to prevent bacterial meningitis in infants and children (Reference 80). Refer to the Pediatric Vaccines chapter for further information on specific vaccinations.

Conclusions

Bacterial meningitis is a medical emergency requiring prompt diagnosis and treatment. The exact pathophysiology of the disease has yet to be elucidated, but evidence supports the theory of nasopharyngeal colonization leading to bacteremia and eventual penetration of the meninges. Without a true understanding of the development of the disease, regardless of improvements in diagnostic testing, accurate diagnosis of bacterial meningitis remains a challenge. Nevertheless, the timely use of appropriate antibiotic therapy and dexamethasone has resulted in improved outcomes through the years, but morbidity and mortality in young infants and children remain high. The most effective means of reducing morbidity and mortality from the disease is prevention of the disease through the development and implementation of effective conjugate vaccines.

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CHAPTER 36

Acute Otitis Media and Upper Respiratory Tract Infections

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Learning Objectives

1. Compare and contrast the etiologic pathogens causing upper respiratory tract infections (URTIs), including acute otitis media (AOM), rhinosinusitis, and pharyngitis.
2. Explain recent trends in antimicrobial resistance among bacterial respiratory tract pathogens.
3. Counsel parents and caregivers on the importance of the judicious use of antibiotics and symptomatic medications, including antipyretics, decongestants, and antihistamine, by pediatric age groups.
4. Discuss scenarios when you would or would not recommend the use of a cephalosporin in a child with a penicillin allergy.
5. Formulate a therapeutic plan for a given case study of a patient with a URTI, including AOM, rhinosinusitis, and pharyngitis.

List of Abbreviations

ABRS	Acute bacterial rhinosinusitis
AOM	Acute otitis media
CMV	Cytomegalovirus
DRSP	Drug-resistant *Streptococcus pneumoniae*
EBV	Epstein-Barr virus
GAS	*Streptococcus pyogenes* or group A β-hemolytic *Streptococcus*
HSV	Herpes simplex virus
RADT	Rapid antigen detection test
TMP/SMX	Trimethoprim/sulfamethoxazole
URTI	Upper respiratory tract infection

Introduction

Acute otitis media (AOM) and upper respiratory tract infections (URTIs), including rhinosinusitis and pharyngitis, are common infections affecting different pediatric groups. Although AOM and rhinosinusitis peak in infants and young children, pharyngitis occurs more frequently in children older than 5 years. Both viruses and bacteria may cause these infections; therefore, antibiotic therapy should be carefully selected for those with true infection of bacterial origin or those at risk of serious complications. The most common bacterial etiologies for AOM and rhinosinusitis are *Streptococcus pneumoniae*, *H. influenzae*, and *M. catarrhalis*. *Streptococcus pyogenes* is the most common bacterial cause of pharyngitis. Some infections may be self-limiting and resolve without treatment. As such, watchful waiting to delay or minimize the use of antibiotics is a prudent strategy for these infections, particularly AOM, without adversely influencing the clinical course. However, because pharyngitis caused by *S. pyogenes* can progress to potentially fatal complications, antibiotic treatment should ensue after confirmed diagnosis.

Acute Otitis Media

Acute otitis media is an infection of the middle ear characterized by middle ear effusion, inflammation, and acute onset of symptoms. It is the most common diagnosis leading to antibiotic prescription in children (References 1, 2). Because the incidence of AOM peaks in infants and young children between 6 months and 2 years of age, 80%–90% of children will have at least one episode by 2–3 years of age (References 3–5). Complications of AOM may occur that consist of temporary hearing impairment, which may delay speech, language, and cognitive abilities; perforation of the tympanic membrane; and intracranial suppurative complications such as meningitis and brain abscess (Reference 6). Temporary hearing loss, caused by the presence of fluid in the middle ear, is the most common complication. In contrast, intracranial complications seldom occur.

The immature immune systems and the function of the eustachian tube predispose young children to AOM. In particular, the angle of the opening of the eustachian tube is decreased in young children. This allows nasopharyngeal bacteria to ascend to the middle ear cavity and prevents adequate drainage of middle ear fluid, both resulting in infection. The anatomic features of the eustachian tubes, together with other risk factors, are associated with the development of otitis media (Box 1) (References 3, 7). Around 37% of children with recent viral URTIs, particularly caused by rhinovirus and adenovirus, will subsequently develop AOM, showing that a viral URTI is an important risk

Box 1. Risk factors associated with otitis media.

- Young age, especially < 2 years
- Day care attendance
- Recent viral upper respiratory illness
- Nasopharyngeal colonization with middle ear bacterial pathogens
- Tobacco smoke exposure
- Bottle-feeding
- Pacifier use
- Sick sibling(s) in household
- Native American, Eskimo, and Australian ethnicities
- Allergies to foods or airborne particles
- Familial predisposition
- Immunodeficiency
- Cleft palate or other craniofacial abnormalities
- Male sex
- Low socioeconomic status

factor for AOM (Reference 5). In addition, exposure to tobacco smoke, allergies to food or airborne particles, and attendance in day care should be evaluated in every child with AOM. If modifiable, exposure to these risk factors should be minimized.

Although viruses, including respiratory syncytial virus, rhinoviruses, influenza, and adenoviruses, cause 20% of AOM cases, the most common etiologies in the United States are bacterial and include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (References 8, 9). Bacteria that infrequently cause AOM are atypical pathogens, group A *Streptococcus*, and gram-negative organisms including *Pseudomonas aeruginosa* (References 7, 10). Mixed infections caused by both bacterial and viral respiratory tract pathogens can occur in up to two-thirds of cases (Reference 11).

Widespread immunization with the heptavalent pneumococcal conjugate vaccine, which covers 60%–70% of the pneumococcal serotypes isolated in AOM, has contributed to the changing epidemiology of bacterial AOM. Certain *S. pneumoniae* serotypes not contained in this vaccine, like serotypes 6C and 19A, have become more prevalent in the United States and worldwide (References 12–17). In addition, penicillin-resistant pneumococcal strains significantly increased from 4% to 13% between 2000 and 2008 (Reference 13). Furthermore, nontypeable *H. influenzae* strains have now become the predominant pathogen causing AOM (References 13, 14). Introduced in the United States in 2010, the 13-valent pneumococcal vaccine provides coverage against all the serotypes available in the 7-valent vaccine, with additional coverage against 19A and potentially 6C through cross-protection (Reference 12). This new pneumococcal vaccine, together with vaccines for *M. catarrhalis* that are under development, will continue to change the microbiology of AOM (Reference 18).

Antimicrobial resistance among the common bacterial respiratory tract pathogens has become a major public health concern during the past decades. In the 1960s, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* were susceptible to penicillin. However, today, all of these bacteria have developed resistance to penicillin. In fact, a significant proportion of *H. influenzae* (30%–50%) and *M. catarrhalis* (more than 90%) isolates cultured from the effusions of children with otitis media in the United States produce β-lactamases (Reference 19). As such, β-lactamase/inhibitor combinations (e.g., amoxicillin with clavulanate), cephalosporins (specifically, ceftriaxone, cefixime, and cefdinir), and fluoroquinolones retain excellent activity against these pathogens. The prevalence of resistance to trimethoprim/sulfamethoxazole (TMP/SMX) among the *H. influenzae* isolates obtained worldwide was 17% between 1998 and 2000 (Reference 20).

Alteration of the penicillin-binding proteins, a resistance mechanism acquired by pneumococci, renders the organism resistant to penicillins, cephalosporins, and other β-lactam antibiotics. In the United States, the prevalence of penicillin-nonsusceptible (including resistant and intermediately susceptible) strains of *S. pneumoniae* reached 42% in 2009 (Reference 21). *S. pneumoniae*, now termed *drug-resistant* S. pneumoniae (DRSP), has developed resistance beyond just penicillin. Resistance or reduced susceptibility has developed to other antibiotics, namely cephalosporins, macrolides (including clarithromycin and azithromycin), tetracyclines, and TMP/SMX (References 20–22). Cross-resistance between erythromycin and clindamycin, which is mediated by the *erm*B ribosomal methylation mechanism (MLS_B-phenotype) that inhibits binding of the antibiotic to the target site, was observed in 32% of *S. pneumoniae* isolates in the United States (References 20, 23). Resistance to fluoroquinolones has been reported, partly because of their extensive use for community-acquired respiratory tract infections, but the incidence remains low (References 24, 25). With respect to age, the prevalence of DRSP appears to be higher in children than in adults and, in fact, peaks in patients younger than 2 years (Reference 26).

Clinical Presentation and Diagnosis

Middle ear effusions with acute onset of symptoms—including fever, rhinorrhea, irritability, otalgia (or ear pain), tugging or rubbing of the ear, and other nonspecific symptoms—are presenting attributes of AOM

(Reference 10). In contrast to AOM, otitis media with effusion refers to uninfected middle ear effusion (i.e., presence of fluid in the middle ear cavity) without acute onset of symptoms, and it can precede or follow AOM.

On otoscopic examination for AOM, the tympanic membrane typically appears erythematous, cloudy, white, or pale yellow. The presence of middle ear effusion is evident by changes in the tympanic membrane including bulging or fullness into the external auditory canal, impaired or absent mobility, and otorrhea (References 10, 27). A bulging tympanic membrane is most characteristic of acute inflammation and therefore AOM (Reference 27). Acute perforation with purulent otorrhea is diagnostic for AOM once otitis externa has been excluded.

The diagnosis of AOM is primarily based on clinical presentation with otoscopic examination, and it should follow stringent criteria to ensure diagnostic accuracy and judicious use of antibiotics. Two significant challenges in diagnosing AOM are establishing the presence of middle ear effusion and distinguishing it from otitis media with effusion (Reference 10). Consequently, some uncertainty exists when diagnosing AOM centered on clinical signs and symptoms. To determine the actual etiology, aspiration of the middle ear fluid (also called tympanocentesis) for culture can be performed. However, this is reserved for special cases, including children who are toxic appearing or unresponsive to several courses of empiric antibiotic therapy.

Treatment

The therapeutic goals for AOM include alleviating symptoms (excluding middle ear effusion), preventing recurrence, using antibiotics judiciously, ensuring patient adherence, and preventing adverse drug reactions. In many cases, the presenting symptoms of AOM usually resolve within 2–3 days after onset. However, middle ear effusion can persist for weeks to months in up to 70% of children (Reference 28). Middle ear effusion has been associated with temporary hearing loss; however, of note, prolonged middle ear effusion alone is not AOM and does not require the use of antibiotics. If antibiotics are used, medication nonadherence, likely because of poor taste, is an issue that should be considered when treating a pediatric patient. Several methods are suggested to improve adherence to prescribed therapies (Box 2).

Nonpharmacologic Therapy

Mild cases of AOM are self-limiting. Even when left untreated, clinical symptoms improve in the first 24 hours and without any major adverse sequelae in most of these cases (Reference 10). As such, initial observation has been widely accepted by the medical community to promote judicious antibiotic use. Initial observation allows a delay in antibiotic therapy, if even necessary, for up to 48–72 hours in some children with AOM (Reference 10). The American Academy of Pediatrics endorses initial observation based on certainty of diagnosis, age, and severity of illness. A certain diagnosis of AOM requires meeting all three criteria: rapid onset of symptoms, middle ear effusion, and middle ear inflammation. For age, initial observation is warranted in children 2 years and older with uncertain diagnosis and in those 6 months to 2 years with uncertain diagnosis and presenting with nonsevere infection (defined as mild otalgia or temperature not exceeding 102.2°F [39°C] in the previous 24 hours) (Reference 10). Appropriate follow-up mechanisms should be in place to monitor children if initial observation is employed (Reference 29).

One primary concern with initial observation is its effect on the clinical course of infection. Mild infections in most children will resolve spontaneously without the need for antibiotic therapy. However, children with AOM who do not improve must subsequently receive antibiotic treatment, with a potential delay of up to 3 days. Compared with those receiving immediate therapy, children with non-severe AOM who received delayed antibiotic therapy experienced more pain initially and took longer to recover from symptoms (References 30, 31). However, these symptoms resolved, regardless of antibiotic use, within 7–10 days. Although symptomatic control was achieved faster than with delayed therapy, immediate antibiotic treatment resulted in more drug-related adverse events and nasopharyngeal carriage of multidrug-resistant *S. pneumoniae* on day 12 (Reference 31). Clinic and emergency department visits, days of missed work or school, and parent satisfaction were unaffected by delayed antibiotic therapy (References 30, 31). Furthermore, delayed therapy is not associated with an increase in mastoiditis in children older than 2 years (Reference 32). In children with severe AOM admitted to the emergency department, reduction in antibiotic prescribing for AOM because of the initial observation strategy was not associated with any adverse outcomes (Reference 33).

Pharmacologic Therapy

Antibiotic treatment should be initiated immediately in children with severe disease (i.e., bulging tympanic membrane with apparent pus, severe otalgia, or temperature of 102.2°F [39°C] or greater). In addition, a child younger than 6 months is usually at increased risk of a more serious infection and therefore should always be initiated on antibiotic therapy, even if the diagnosis is uncertain (Reference 10). Most clinical symptoms, except for middle ear effusion, resolve within 48–72 hours after antibiotic initiation. Of note, persistent middle ear effusion is not indicative of treatment failure.

Box 2. Medication adherence and counseling tips.

Tips to improve adherence to oral medications in children

- Use flavoring services offered by pharmacies, or mix with small amounts of juice or milk to improve palatability.
- Use oral syringes to easily extract the medication dose. Quickly push the plunger in so that the liquid squirts on the inner cheek. Blowing on the child's face can facilitate swallowing.
- Use oral suspensions for a child younger than 2 years. Chewable tablets may be tolerated by some 2-year-old children. Most children will be unable to swallow tablets or capsules until they are 8 years old.
- Acetaminophen suppositories should be considered for an uncooperative child.

Important counseling points for parents and caregivers

- Antibiotics do NOT cure viral infections (like the cold or flu), nor do they relieve fever or pain.
- Mild cases of acute otitis media will resolve without antibiotic use.
- Observation for 48–72 hours is an acceptable alternative to antibiotic treatment in older children with mild symptoms of acute otitis media. If the child does not improve within 48–72 hours, follow up with the pediatrician.
- When an antibiotic is prescribed, provide dosing instructions and emphasize the importance of completing the full course of antibiotic to successfully treat the infection and prevent the development of antibiotic resistance. Instruct on the common adverse effects of the prescribed antibiotic (as noted in Table 1).
- Ensure that the duration of antibiotic therapy is 10 days for any child younger than 2 years.
- Relieve anxiety about a febrile child. Explain that fever is a natural body response to infection and that it will not harm the child.
- When recommending acetaminophen or ibuprofen for fever or ear pain, provide clear instructions on the following points:
  - Ensure that parents understand how much to give, expressed in both milligrams and milliliters. Infant formulations are more concentrated and thus require less volume per dose.
  - Optimize the dose for fever control. In general, ibuprofen 10 mg/kg is about equal to acetaminophen 15 mg/kg (Reference 49). Acetaminophen can be administered as often as every 4 hours (not to exceed five doses in 24 hours) and ibuprofen as often as every 6 hours.
  - Discourage methods of alternating acetaminophen and ibuprofen unless clear verbal and written instructions are provided.
- Encourage routine childhood vaccinations using the schedule recommended by the Centers for Disease Control and Prevention. Be prepared to recommend local clinics and pharmacies that provide immunizations. Identify and recommend the annual flu vaccine for all people at high risk of complications from influenza infection.

Resources for additional information

- "Get Smart: Know When Antibiotics Work" by checking the Web site of Centers for Disease Control and Prevention (www.cdc.gov/getsmart/).
- Check the official Web site of the American Academy of Pediatrics.

Antibiotic therapy is generally empiric and usually involves the use of oral agents. High-dose amoxicillin, defined as 80–90 mg/kg/day, is the first-line treatment, with a reported response rate of greater than 80% (Table 1) (Reference 10). High-dose amoxicillin achieves elevated drug concentrations in the middle ear to consequently provide activity against intermediately susceptible and many resistant *S. pneumoniae* (Reference 34). The most common adverse effects are gastrointestinal tract–related, including nausea and diarrhea. The incidence of adverse effects associated with high-dose amoxicillin is comparable to that of standard-dose amoxicillin (Reference 35). Compared with twice-daily dosing, however, three times/day-dosing of high-dose amoxicillin is associated with a significantly higher incidence of diarrhea (Reference 36).

Adding clavulanic acid to high-dose amoxicillin or changing to ceftriaxone (intramuscular injection) can be considered if the patient does not respond to high-dose amoxicillin (References 10, 37). Other candidates for these antibiotics include children with antibiotic exposure within the previous 30 days and children in whom *H. influenzae* or *M. catarrhalis* infection is suspected. The addition of clavulanic acid, or substitution with a cephalosporin, enhances activity against β-lactamase–producing *H. influenzae* and *M. catarrhalis*. Oral cephalosporins including cefuroxime axetil, cefdinir, and cefpodoxime are other treatment options.

The standard duration of antibiotic therapy, particularly for children who are younger than 2 years or have severe disease, is 10 days (Reference 29). However, a shorter course of 5–7 days is an option for children with mild disease, particularly those 6 years and older

Table 1. Antibiotic Treatment Options for Upper Respiratory Tract Infections in Children[a]

Infection Type	Common Causative Bacterial Pathogens	Recommended Therapy	Alternative Therapy	Common Adverse Effects
Acute otitis media	*Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*	High-dose amoxicillin 80–90 mg/kg/day divided in two or three doses[b]	High-dose amoxicillin 80–90 mg/kg/day with clavulanate 6.4 mg/kg/day divided in two doses[b]	Diarrhea and allergic reactions (including Stevens-Johnson syndrome)
			Ceftriaxone 50 mg/kg/day intramuscularly once daily for 1- 3 days [c]	Pain at injection site, allergic reactions, diarrhea, and gallbladder sludging
			Azithromycin 10 mg/kg/day once daily for 3 days (maximum 500 mg/day); or 15 mg/kg on day 1, followed by 5 mg/kg/day as a single dose for 4 days; or 30 mg/kg as one dose on a single day (maximum 1,500 mg)[d]	Diarrhea, abdominal pain, nausea, and vomiting
			Clarithromycin 15 mg/kg/day divided in two doses[d,e]	Diarrhea, abdominal pain, nausea, vomiting, and drug interactions
			Clindamycin 30–40 mg/kg/day divided in three doses[d,f]	Diarrhea and pseudomembranous colitis
			Levofloxacin 6 months to 5 years old: 20 mg/kg/day divided in two doses; > 5 years old: 10 mg/kg/day once daily (maximum 500 mg/day)[g]	Musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality); vomiting and diarrhea
Acute bacterial rhinosinusitis	*S. pneumoniae, H. influenzae*, and *M. catarrhalis* (less common anaerobic bacteria, *Streptococcus* spp. and *Staphylococcus aureus*)	Amoxicillin-clavulanate 45 mg/kg/day, divided in two doses[b,h]	Amoxicillin-clavulanate 90 mg/kg/day, divided in two doses[b,h]	Diarrhea and allergic reactions (including Stevens-Johnson syndrome)
			Ampicillin-sulbactam 200–400 mg/kg/day intravenously divided every 6 hours	Rash and diarrhea
			Ceftriaxone 50 mg/kg/day intravenously or intramuscularly once or twice daily[i]	Pain at injection site, allergic reactions, diarrhea, and gallbladder sludging
			Cefotaxime 100–200 mg/kg/day intravenously or intramuscularly divided every 6–8 hours[i]	Rash and diarrhea
			Clindamycin 30–40 mg/kg/day in three divided doses plus cefixime 8 mg/kg/day in two divided doses, or cefpodoxime 10 mg/kg/day in two divided doses[f]	Diarrhea and pseudomembranous colitis (clindamycin); rash and diarrhea (cephalosporins)
			Levofloxacin 10–20 mg/kg/day every 12–24 hours[d] (intravenous route recommended for hospitalized patients)	Tendonopathy, arthritis, or arthralgia of weight-bearing joints

Acute pharyngitis	*Streptococcus pyogenes* (or group A β-hemolytic *Streptococcus*)[j]	Oral penicillin V (phenoxymethyl penicillin) ≤ 27 kg: 250 mg (400,000 units) two or three times/day for 10 days; > 27 kg: 250 mg (400,000 units) four times/day, or 500 mg (800,000 units) two times/day	Intramuscular benzathine penicillin[k] ≤ 27 kg: 600,000 units as a single dose > 27 kg: 1,200,000 units as a single dose	Allergic reactions (including anaphylaxis), pain at injection site (if applicable), serum sickness–like reactions, and diarrhea
			Amoxicillin 50 mg/kg/day orally as a single dose (maximum 1,000 mg) or in two divided doses ≥ 12 years: 775-mg extended-release tablet once daily with meals; 875 mg twice daily, or 500 mg three times/day	Diarrhea and allergic reactions (including Stevens-Johnson syndrome)
			Ampicillin 50–100 mg/kg/day in three or four divided doses	Diarrhea and allergic reactions (including Stevens-Johnson syndrome)
			Cephalexin 40 mg/kg/day in two divided doses (maximum 1,000 mg/day)[l]	Rash and diarrhea
			Cefadroxil 30 mg/kg once daily (maximum 1,000 mg)[l]	Rash and diarrhea
			Azithromycin 12 mg/kg once daily for 5 days (maximum 500 mg/day); 500 mg on day 1, followed by 250 mg/day on days 2–5[d,m]	Diarrhea, abdominal pain, nausea, and vomiting
			Clindamycin 20 mg/kg/day in three divided doses (maximum 900 mg/day)[d,f]	Diarrhea and pseudomembranous colitis

[a]All antibiotic dosing regimens are based on normal renal and hepatic functions. All antibiotics are available in oral formulations except for ceftriaxone, cefotaxime, and penicillin G benzathine.
[b]To minimize diarrhea, the maximal recommended daily dose of amoxicillin is 3–4 g, and twice-daily administration is preferred for high-dose amoxicillin with clavulanic acid.
[c]Ceftriaxone may be useful for nonadherent patients, and its duration varies from 1 to 3 days. Ceftriaxone provides sufficient antibiotic concentrations in the middle ear for activity against penicillin-nonsusceptible *S. pneumoniae.* Oral cephalosporins, including cefuroxime axetil 30 mg/kg/day, cefdinir 14 mg/kg/day, and cefpodoxime 10 mg/kg/day, can be alternatively used but may not achieve adequate concentrations.
[d]Safe alternatives for severe or type I hypersensitivity reactions to penicillin or cephalosporins.
[e]Together with reduced activity against *H. influenza* among macrolides, resistance limits their clinical utility. Clarithromycin has many significant drug interactions.
[f]Although clindamycin is active against drug-resistant *S. pneumoniae*, 22 to 31% of strains are resistant (Reference 21, 71).
[g]Since not approved for acute otitis media, it should be reserved for persistently recurrent otitis media.
[h]High-dose amoxicillin with clavulanate should be reserved for children with antibiotic exposure within the past 30 to 90 days, recent hospitalization, severe symptoms, < 2 years of age, day-care attendance, or residing in regions with penicillin-nonsusceptible *S. pneumoniae* ≥ 10%.
[i]For children with vomiting that precludes the use of oral antibiotics. Conversion to an oral antibiotic should be instituted within 24 hours or on resolution of vomiting (whichever is earlier).
[j]Although viruses and other bacteria may cause acute pharyngitis, antimicrobial treatment is indicated for group A *Streptococcus* (GAS). To successfully eradiate GAS, oral antibiotics should be administered for 10 days (unless otherwise indicated).
[k]Indicated for those who cannot complete or tolerate a 10-day course of oral therapy, or those at increased risk of acute rheumatic fever. The formulation of benzathine penicillin G 900,000 units (562.5 mg) with procaine penicillin G 300,000 units (187.5 mg) is recommended for children weighing 27 kg or less. The efficacy of this combination for adolescents weighing more than 27 kg and adults has not been shown. The sites for intramuscular administration are the mid-lateral aspect of the thigh for infants and small children and the upper, outer quadrant of the buttock for adolescents and adults.
[l]Other oral cephalosporins are acceptable alternatives, including cefprozil, cefaclor, cefuroxime, cefdinir, cefpodoxime, cefixime, and ceftibuten. Therapy duration is 5 days for cefpodoxime and cefdinir and 10 days for all other cephalosporins.
[m]Use should be based on local resistance patterns. Erythromycin or clarithromycin for 10 days is an alternative. However, erythromycin is associated with a high incidence of gastrointestinal adverse effects.

(References 10, 37). The only exceptions are ceftriaxone for 1–3 days and azithromycin for 3–5 days, depending on the severity of disease and persistence of symptoms.

The high prevalence of resistance to TMP/SMX and erythromycin by DRSP hinders the utility of these antibiotics (Reference 34). At least 80% of DRSP are resistant to TMP/SMX and 50% to erythromycin (Reference 38). In addition, TMP/SMX has limited activity against group A *Streptococcus* that can cause AOM associated with perforation of tympanic membranes. Pediazole (contains sulfisoxazole and erythromycin) may be considered in geographic regions with a low prevalence of DRSP and is a safe alternative in children with a history of hypersensitivity reactions to penicillin. Nonetheless, these agents are not recommended in children whose high-dose amoxicillin therapy has failed.

Judicious Antibiotic Use

The use of antibiotics comes with risks, which must be carefully considered and recognized by both health care professionals and parents (Table 1). In addition to its contribution to the increasing prevalence of antimicrobial resistance, antibiotic use can lead to adverse drug reactions. In fact, antibiotics were categorized as the No. 1 cause of adverse drug reactions in hospitalized children (Reference 39). Among specific antibiotics, penicillins and cephalosporins most often contributed to the adverse events. Specifically, children with AOM treated with antibiotics have more adverse effects than those untreated (Reference 37).

Although hospitals have implemented antimicrobial stewardship programs to optimize antimicrobial use, these efforts in the outpatient and community settings can be improved (Reference 40). Not all infections require antibiotics, an important concept embraced and promoted by the Centers for Disease Control and Prevention through its Get Smart campaign. Specifically for AOM, initial observation should be considered in certain cases to increase efforts toward judicious antibiotic use. If antibiotics are prescribed, proper drug, dose, and duration should be reviewed for age appropriateness. In addition to antibiotic therapy, recommendations for over-the-counter medications to control symptoms, like ear pain and fever, may be necessary. When recommending these products, providers must give clear instructions on dosing and ensure that parents and caregivers understand that the various nonprescription drug formulations are not interchangeable (Box 2).

Penicillin Allergy

The use of amoxicillin or cephalosporins may present a dilemma in a child with penicillin allergy. The risk of cross-reactivity to cephalosporins is increased in children with a history of penicillin allergy and between different cephalosporins, particularly first-generation cephalosporins (References 41, 42). Based on a review of seven studies, the cross-reactivity to cephalosporins in patients with positive penicillin skin tests is 4.4%, not 10%–15% as previously suggested by retrospective studies that lacked routine skin testing (Reference 43). Furthermore, cross-sensitivity is insignificant with second- and third-generation cephalosporins in children with penicillin allergy (Reference 42). A prospective study of children reported 30% cross-reactivity to cephalosporins among those with penicillin allergy (Reference 41). These data suggest that most children with a history of mild reactions to penicillin will tolerate cephalosporins.

Although most children with mild penicillin allergy will tolerate cephalosporins, the safety of administering cephalosporins remains uncertain. Assessing the timing (including first-dose response) and nature of the penicillin allergy to determine the presence of potentially life-threatening type I, immunoglobulin E (IgE)-mediated hypersensitivity reaction is critical in making the clinical decision of whether to expose a child to a cephalosporin (Reference 44). If a child has a non-life-threatening or mild reaction to penicillin (including morbilliform rashes commonly reported with amoxicillin), then a cephalosporin (e.g., cefdinir, cefpodoxime, cefuroxime, or ceftriaxone) may be considered because serious reactions to cephalosporins are rare (References 10, 45). In contrast, if the child develops an IgE-mediated hypersensitivity reaction (i.e., urticaria or anaphylaxis) that is considered life threatening, both amoxicillin and cephalosporins should be avoided.

In evaluating an antibiotic allergy, obtaining an accurate medical history is essential to distinguish true hypersensitivity reactions from other, less severe adverse reactions (Reference 44). A non-β-lactam antibiotic should be selected in children with IgE-mediated hypersensitivity reactions or perhaps when the nature of the reaction or history of penicillin allergy is uncertain. Treatment options include macrolides (specifically, azithromycin and clarithromycin) and clindamycin. Clarithromycin and azithromycin possess activity against *S. pneumoniae*, *H. influenzae, M. catarrhalis,* and atypical respiratory pathogens. A recent study showed similar effectiveness, but with fewer adverse effects and improved adherence, between a single 60-mg/kg dose of azithromycin and a 10-day course of high-dose amoxicillin with clavulanate in children with AOM (Reference 46).

Although they are not β-lactam antibiotics, the high prevalence of resistance to Pediazole (which contains erythromycin and sulfisoxazole) and the risk of cartilage toxicity associated with fluoroquinolones (particularly levofloxacin) limit their utility for routine use in children with AOM. However, levofloxacin may play a role in children with persistent and recurrent AOM even though it is not an approved indication. Tympanocentesis should be performed first to determine the causal pathogen; subsequently, tympanostomy tube placement or therapy with levofloxacin, especially for susceptible isolates, can be considered (Reference 47).

Adjunctive Therapy

A child with AOM may present with fever. Hence, it is important to instruct parents on the appropriate use of antipyretic medications (Box 2). A fever is defined as an elevation in body temperature exceeding 100°F by mouth (100.4°F rectally) and is mediated by an increase in the hypothalamic heat regulatory set point regulated by prostaglandins. Acetaminophen 10–15 mg/kg given every 4–6 hours can be administered orally to children of all ages and is considered the agent of choice for infants younger than 6 months. Alternatively, ibuprofen 5–10 mg/kg administered orally every 6–8 hours can be used for children older than 6 months.

According to a meta-analysis, ibuprofen may be more effective than acetaminophen as an antipyretic, particularly in sustaining this effect (Reference 48). However, this speculation was based on studies with small sample sizes and assessing the effect of a single dose. Although it can be administered in infants younger than 6 months, acetaminophen does not have an anti-inflammatory effect, which is present in ibuprofen.

Several methods exist for alternating antipyretics (e.g., interchanging acetaminophen and ibuprofen every 2–3 hours, or acetaminophen every 4 hours within ibuprofen every 6 hours). These methods contain inherent flaws, including surpassing the five-dose daily allowance of acetaminophen, inappropriately shortening the frequency of ibuprofen at every 4 hours, and administering both medications at two same time points within a 24-hour period (Reference 49). Together with the lack of evidence for efficacy, the primary concern for alternating antipyretics is potential dosing errors. Dosing errors can lead to intoxication or hepatotoxicity from acetaminophen or nonoliguric renal dysfunction from ibuprofen. Providing a thorough education to parents and caregivers on the appropriate use of antipyretics is imperative for preventing dosing errors and is a critical role that health care professionals can assume (Box 2).

A child with AOM usually presents with ear pain. Assessment and treatment of pain should be provided for all patients with AOM (Reference 10). For mild to moderate pain, acetaminophen and ibuprofen are equally effective. Codeine may be required for the management of moderate to severe pain. Otic products, including aqueous lidocaine (lignocaine) and herbal extract Otikon, require additional studies to ascertain their effectiveness for pain relief in children. In the presence of heavy middle ear effusion, draining this fluid may relieve the pain caused by the fluid pressure.

Antihistamines and decongestants for symptomatic relief of AOM have not been well studied. In fact, their use has been associated with increased medication adverse effects (Reference 50). Furthermore, over-the-counter cough and cold medications should not be given to infants and children younger than 2 years because of the risk of life-threatening adverse effects (Reference 51).

Prevention Through Immunization

The two vaccines that have shown effectiveness in preventing AOM are the influenza and pneumococcal vaccines. The influenza vaccine may reduce the occurrence of AOM by 50%, particularly in young children attending day care (Reference 52). The injectable influenza formulations are indicated for infants at least 6 months old, and the intranasal spray is recommended for children older than 2 years. For any child aged 6 months to 9 years who receives the vaccine for the first time, two doses are recommended to enhance immunity (Reference 53).

The 7-valent pneumococcal conjugate vaccine, introduced in the United States in 2000, provides only a modest decrease in the occurrence of AOM, compared with the flu vaccine (Reference 54). However, it may reduce the need for tympanostomy tube placement and nasal carriage of penicillin-nonsusceptible strains (in conjunction with restriction in antibiotic use) in children with AOM (References 54, 55). One study suggested that standard-dose, rather than high-dose, amoxicillin is effective for children with mild cases of AOM who received at least three doses of the pneumococcal conjugate vaccine (Reference 56). Replacing the 7-valent vaccine, the 13-valent pneumococcal conjugate is now recommended for routine immunization in infants. Its effects on the incidence and epidemiology of AOM will remain uncertain until its use becomes widespread.

Prevention of Recurrence

Recurrence, defined as three or more documented episodes within 6 months or four or more episodes within 12 months, can occur in some children, particularly those who first experienced AOM younger than 6 months of age and those with immune deficiencies (e.g., IgG deficiency) or craniofacial abnormalities (e.g., cleft palates) (Reference 57). In addition to first

providing parent education and immunization, antibiotic prophylaxis and surgery—including myringotomy and placement of tympanostomy tubes—are important interventions in children with recurrent AOM.

Antibiotic prophylaxis has been shown to reduce the occurrence of AOM by 20%, where five children need to be treated to prevent one child from experiencing AOM (Reference 58). With this modest benefit, antibiotic prophylaxis should be considered only in selected children with well-documented recurrences of AOM. Children most likely to benefit from prophylactic therapy include those younger than 2 years, day care attendants who cannot modify this risk factor, infants who experienced their first episode of AOM before 6 months of age, and those with developmental or language delays.

When indicated, prophylactic therapy should be initiated in the fall or winter and should continue consistently through the winter season for a maximum of 6 months (Reference 59). Amoxicillin 40 mg/kg once daily is the first-line agent for prophylaxis. Alternatively, sulfisoxazole 50 mg/kg once daily can be used, particularly in a child with a penicillin allergy. In children with breakthrough AOM while receiving antibiotic prophylaxis, a different agent is necessary, like high-dose amoxicillin/clavulanate or ceftriaxone.

Although antibiotic prophylaxis reduces episodes of AOM, this protection wanes once prophylaxis is discontinued (References 58, 60). In addition, prolonged antibiotic use may select for infections caused by resistant nasopharyngeal bacteria (Reference 61). Because of these concerns for waning effectiveness and selection for resistant bacteria, surgical intervention should be considered in children with recurrent AOM.

Myringotomy with tympanostomy tube placement helps drain the copious middle ear fluid that is evident in patients with chronic otitis media. Although it is the treatment of choice for chronic otitis media, tube placement decreases infection rates only modestly in patients with recurrent AOM, especially in the first 6 months after surgery (References 62, 63).

Summary

The treatment modality for AOM does not necessitate the use of antibiotics in all cases. In fact, because AOM is self-limiting, initial observation is warranted for mild cases, and antibiotic therapy should be reserved for those with severe disease or young infants. Although antibiotic therapy improves patient response within 3 days, adverse drug effects may occur. Thus, more studies are needed to ascertain the characteristics of children who will most benefit from antibiotic therapy. Parent or caregiver education on the proper use of antibiotics, if warranted, and other medications for symptomatic relief, including their adverse effects, is critical to ensure optimal management of AOM.

Rhinosinusitis

Sinusitis, an inflammatory process that involves the mucous membranes of both the nose and paranasal sinuses, is more properly termed *rhinosinusitis*. Rhinosinusitis is classified as acute (sudden onset of symptoms with a duration of less than 30 days), subacute (duration of 30 days or more and less than 90 days), or chronic (duration greater than 90 days). Viruses (including the human rhinovirus, influenza A and B viruses, parainfluenza virus, respiratory syncytial virus, adenovirus, and enterovirus) are responsible for most acute cases of rhinosinusitis (also called the "common cold"); most cases are self-limiting and resolve without treatment within 5–10 days after symptom onset.

Acute bacterial rhinosinusitis (ABRS) is a secondary infection that occurs in 8% of children with viral URTI and peaks in the second year of life (Reference 64). In addition to inhibiting macrophage and lymphocyte function, viruses induce inflammatory changes to block the sinus ostia, impair mucous drainage, and cause poor aeration, leading to increased susceptibility to secondary bacterial infection. Day care attendance and allergic rhinitis may also predispose children to ABRS (References 65–67). Because ABRS requires appropriate management to facilitate recovery and prevent orbital and intracranial complications, the following sections will focus strictly on the etiology and management of ABRS, excluding viral rhinosinusitis.

By early childhood, most children are colonized by at least one of three respiratory tract pathogens, including *S. pneumoniae*, *H. influenzae* (nontypeable), and *M. catarrhalis*. These respiratory tract bacteria are the most common causes of ABRS (References 68–70). The prevalence of *H. influenzae* increased and *S. pneumoniae* decreased after routine pneumococcal vaccination in children in the United States (Reference 71). As such, the production of β-lactamases that are common in *H. influenzae* limits the clinical utility of amoxicillin alone compared with amoxicillin plus clavulanate. Similar to AOM, anaerobic bacteria, *Staphylococcus aureus*, and *S. pyogenes* can also cause ABRS, although less commonly. The clinical significance of atypical pathogens, including *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, in the pathogenesis of ABRS remains unclear.

Inflammation of the paranasal sinuses exceeding 90 days is considered chronic rhinosinusitis and should be distinguished from ABRS. In contrast to ABRS, the pathogenesis of chronic rhinosinusitis is believed to be multifactorial, with potential causes including microorganisms (bacteria, fungi), inflammatory agents (e.g.,

allergens, pollutants, smoke), asthma, cystic fibrosis, gastroesophageal reflux, immunodeficiency, and nasal polyposis (References 66, 68, 70). These factors may appear concurrently to cause persistent inflammation of the nose and paranasal sinuses.

Clinical Presentation and Diagnosis

Evidence of respiratory symptoms, including nasal discharge and congestion, with or without daytime cough are the clinical features of ABRS. The nasal discharge may be watery, serous, or purulent. Of importance, purulent nasal secretions and a change in the color of nasal discharge are not specific indicators of ABRS. Purulent discharge can also occur in patients with viral rhinosinusitis. When cough is present, it may be wet or dry, occur during the day, and possibly worsen at night. Fever, sore throat, headache, and malodorous breath may occur together with these cardinal respiratory symptoms (Reference 72). The fever usually subsides within 48 hours when the nasal symptoms become more evident.

A diagnostic challenge of ABRS is that no single sign or symptom clinically distinguishes it from viral rhinosinusitis. Although the clinical presentations of ABRS and viral URTIs are similar, the distinctive characteristics of ABRS are the persistence, severity, and progression (or worsening) of symptoms (Reference 73). Respiratory symptoms in children with ABRS persist without improvement beyond 10 days, unlike viral URTIs, in which symptoms usually abate within 5–10 days (References 70, 71). In addition, a slight improvement that precedes the considerable worsening of symptoms on the sixth or seventh day of illness, known as "double sickening," suggests ABRS (Reference 73). Another indicator of ABRS is the presence of a high fever (defined as a temperature of 102.2°F [39°C] or higher) with purulent nasal discharge, or facial pain for 3 or more consecutive days (Reference 71).

Diagnosis of ABRS is generally based on clinical presentation noted as persistent, worsening, or severe symptoms that extend beyond 10 days. Although no single sign or symptom is highly sensitive or specific, the presumptive diagnosis of ABRS based on the overall constellation of clinical findings is generally sufficient for treatment. Viral or allergic etiologies that may present similarly to ABRS should be excluded. Sinus aspiration with positive microbiologic culture results definitively confirms a diagnosis of ABRS. However, because this procedure is invasive and requires a skilled specialist, it is not routinely performed.

The use of imaging studies (radiography, computerized tomography [CT], or magnetic resonance imaging) is unnecessary to confirm the diagnosis because abnormal findings indicate the presence of inflammation without providing the cause (i.e., virus, bacteria, or allergy). Radiologic examination is recommended only in children with suspected orbital or intracranial complications associated with ABRS, or in those with persistent or recurrent infection who are unresponsive to therapy (References 70, 71). A sinus CT scan is the imaging study of choice because it is more sensitive and specific than plain radiographs (Reference 71).

In children with inadequate treatment, complications of ABRS may occur and can range in severity from mild, such as periorbital cellulitis, to serious, including orbital cellulitis, osteomyelitis of the frontal bone, meningitis, and epidural or brain abscess (References 69, 70, 74). Immediate aggressive medical therapy, which may include surgery, is necessary, especially if abnormal vision, altered mental status, and periorbital edema are presenting symptoms (Reference 75).

Treatment

Symptomatic relief, prevention of complications, and minimization of adverse drug effects are the primary goals of antibiotic therapy in children with ABRS. Although the effectiveness of antibiotic therapy in preventing complications remains uncertain, it appears to improve clinical cure rates (References 71, 76).

Pharmacologic Therapy

Antibiotic treatment of ABRS should target the common etiologic culprits, particularly *S. pneumoniae, H. influenzae*, and *M. catarrhalis*, and account for resistance patterns among these pathogens (as described in the previous section on AOM). Overuse of antibiotics has contributed to the emergence and increasing prevalence of resistance in the United States. To address resistance, the most recent guidelines for the treatment of acute rhinosinusitis focus on the judicious use of antibiotics (Reference 70).

Because of its safety, palatability, and low cost, amoxicillin with clavulanate is recommended by the Infectious Diseases Society of America as first-line therapy in children (Table 1). Dosing of the amoxicillin component should depend on the potential for drug-resistant pneumococci (e.g., recent antibiotic exposure, day care attendance) and severity of illness. High-dose amoxicillin with clavulanate is recommended for children with severe symptoms (including a temperature of 102.2°F [39°C] or greater with concurrent purulent nasal discharge for at least 3–4 consecutive days), with recent hospitalization or antibiotic exposure, who are younger than 2 years, who attend day care, or who reside in regions with penicillin-nonsusceptible *S. pneumoniae* at 10% or greater (References 70, 71). When high-dose amoxicillin is used with clavulanate, the recommended dose of clavulanate is 6.4 mg/kg/day to limit the occurrence of diarrhea (Reference 76).

When *H. influenzae* or *M. catarrhalis* is highly suspected, the use of amoxicillin alone is ineffective because most isolates produce β-lactamases. Treatment options consist of amoxicillin with clavulanate or cephalosporins. Third-generation cephalosporins (specifically, cefixime and cefpodoxime), in addition to clindamycin, are alternatives to amoxicillin with clavulanate. Otherwise, a single dose of ceftriaxone can be administered either intravenously or intramuscularly when oral therapy is not possible. Although treatment most often occurs in the outpatient setting, seriously ill children with ABRS should be hospitalized for intravenous antibiotics, including ampicillin-sulbactam, cefotaxime, ceftriaxone, or levofloxacin.

Concern for musculoskeletal adverse effects associated with levofloxacin limits its use to children with immediate type I hypersensitivity to β-lactam antibiotics. Except for those with a history of true type I hypersensitivity to β-lactams, children with other types of reactions to a specific β-lactam antibiotic may tolerate another β-lactam. Macrolides, doxycycline, and TMP/SMX are not routinely used in children because of concern about treatment failures, based on susceptibility patterns. Doxycycline is also contraindicated in children 8 years and younger because of the risk of permanent teeth discoloration.

Telithromycin, the first agent in a class of antibiotics called the ketolides, was developed to address macrolide-resistant *S. pneumoniae* (Reference 59). In the presence of the *erm*B gene (and, for telithromycin, the *erm*B and *mef*A genes), ketolides remain active against macrolide-resistant pathogens (Reference 60). Although similar to the macrolides, telithromycin binds more tightly to the 50S ribosomal subunit to enhance activity against respiratory pathogens (Reference 61). Although telithromycin is approved by the U.S. Food and Drug Administration for the treatment of ABRS, it is not indicated for pediatric use. The most common adverse effects reported have been gastrointestinal tract related, including nausea and diarrhea. Furthermore, telithromycin has been associated with life-threatening and fatal hepatic failure. Telithromycin is also contraindicated in patients with myasthenia gravis because of reports of fatal respiratory failure.

Patients generally respond to appropriate treatment within 48–72 hours (Reference 76). The recommended therapy duration for ABRS is 10–14 days, or at least 7 days after clinical improvement begins (References 70, 71). Antibiotic therapy in children with ABRS who are unresponsive 72 hours after treatment initiation should be changed to high-dose amoxicillin with clavulanate or other second-line alternatives, including intravenous formulations, if deemed necessary. If orbital or intracranial complications are suspected, or the use of intravenous antibiotics is contemplated, the diagnosis of ABRS should be confirmed with sinus imaging. In addition, sinus aspiration with subsequent cultures can help identify the causative pathogen and thereby tailor therapy appropriately under these circumstances.

Adjunctive Therapy

Symptomatic relief is one of the goals in the treatment of ABRS. Intranasal budesonide provides a modest reduction in nasal discharge and cough (Reference 77). Similarly, the combination of an antihistamine and decongestant offers minimal symptomatic relief (Reference 78). As such, these adjunctive therapies are not recommended for routine use in children (References 70, 71, 79). However, saline nasal drops, spray, or irrigation helps dissolve secretions and prevent crust formation (Reference 80). Because it possesses minimal risk, saline topical therapy may be used in children for symptomatic relief of nasal symptoms.

Summary

Appropriate management of ABRS requires an understanding of its distinctive pathogenesis and clinical features. In contrast to the common cold and chronic rhinosinusitis, ABRS does not originate from viral or allergic etiologies. In addition, the symptoms of ABRS persist without improvement beyond 10 days and usually completely resolve by 30 days. Even though it is a secondary infection caused by respiratory tract bacterial pathogens, ABRS treatment with antibiotics should be judicious to limit the development of resistance.

Pharyngitis

Pharyngitis, characterized by inflammation of the mucous membranes and structures of the throat, encompasses tonsillitis, tonsillopharyngitis, and nasopharyngitis. It occurs frequently in children and therefore accounts for many annual clinic visits (Reference 81). Although sore throat accompanies pharyngitis, objective findings of erythema, exudates, or ulceration are required for diagnosis. Many etiologic agents or factors have been implicated for pharyngitis, including infectious vehicles, aphthous stomatitis, Behçet syndrome, and Kawasaki disease (Reference 82). Nonetheless, viruses, followed by bacteria, are the most common infectious causes of pharyngitis in children and adolescents. Viral pharyngitis predominates in the summer and fall seasons, whereas bacterial pharyngitis occurs in the late autumn, winter, and spring in temperate climates (Reference 83).

Certain viruses, including the Epstein-Barr virus (EBV), cytomegalovirus (CMV), adenoviruses, herpes simplex virus (HSV), influenza viruses, and enterovirus directly insult the pharynx to elicit inflammation

(Reference 84). Other viruses, including rhinoviruses, coronaviruses, respiratory syncytial virus, and parainfluenza viruses, cause nasopharyngitis. In these cases, the sore throat is not the result of direct pharyngeal insult, but rather, the result of irritation related to mouth breathing or cough caused by rhinorrhea.

Among bacterial pathogens, *S. pyogenes* (group A β-hemolytic *Streptococcus* [GAS]) accounts for up to 37% of all pharyngitis cases in children and adolescents (References 85, 86). As such, it is the most common bacterial cause of pharyngitis, particularly in children older than 5 years (References 86, 87). Penicillin resistance has not been a significant issue for GAS; however, erythromycin resistance has been reported in school-aged children (References 88, 89). Other bacterial culprits of pharyngitis are non-group A *Streptococcus*, *M. pneumoniae*, *Neisseria gonorrhoeae* (particularly in adolescents who engage in oral-genital sex), *Arcanobacterium haemolyticum*, and *Corynebacterium diphtheriae* (Reference 82).

The following sections will accentuate the clinical presentation and therapeutic management of bacterial—particularly streptococcal—pharyngitis. However, distinctive clinical features of viral and bacterial pharyngitis will also be presented because differentiation between the two etiologies is critical to justify the initiation of antibiotic therapy.

Clinical Presentation and Diagnosis

Evidence of erythema, edema, or exudates of the pharynx on physical examination is mandatory for diagnosing acute pharyngitis caused by either viruses or bacteria. Pharyngitis caused by GAS often occurs in school-aged children and adolescents. Rapid onset of symptoms including sore throat, fever, tonsillar exudates, cervical adenopathy, headache, abdominal pain, nausea, and/or vomiting are clinical characteristics of GAS pharyngitis (References 83, 90, 91). An inflamed uvula may also be present. The inception of symptoms is abrupt, and they usually resolve without antibiotic treatment within 3–5 days. In fact, sore throat persisting for greater than 7 days suggests other causes of pharyngitis. Nonetheless, antibiotic treatment is indicated for clinical cases of GAS pharyngitis to minimize progression to serious complications.

Although uncommon, GAS pharyngitis may occur in infants and children younger than 3 years, particularly as outbreaks in child care settings. The clinical presentation in this age group is generally nonspecific and subtle and includes fever, irritability, and anorexia. However, the finding of close contacts (e.g., siblings and day care attendants) with recent GAS infection strongly suggests GAS pharyngitis.

The common features of viral pharyngitis are concurrent conjunctivitis, cough, coryza, diarrhea, anterior stomatitis, ulcerative lesions, and rash (References 57, 81, 83, 92). Certain viruses exhibit unique clinical attributes. For example, infectious mononucleosis caused by EBV and CMV that commonly occurs in adolescents manifests as prolonged exudative pharyngitis, cervical lymphadenopathy, hepatitis, and rash that develops when treated with ampicillin or amoxicillin. Pharyngoconjunctival fever is highly indicative of adenovirus, and herpangina with small vesicles appearing in the posterior pharynx is indicative of coxsackie A viruses (a type of enterovirus). Pharyngitis caused by HSV generally presents with ulcerative lesions of the mouth and lips in young children and adolescents. Finally, the seasonality of infection, in addition to fever, cough, and myalgias, is typical of influenza infection.

Although clinical signs and symptoms may provide evidence for GAS etiology, diagnosis should be validated by throat culture and/or rapid antigen detection test (RADT), ideally before therapy is begun (References 93, 94). In the absence of indicators for viral URTI, candidates likely to have GAS pharyngitis consist of those in recent contact with an individual infected by GAS (including a history of acute rheumatic fever or poststreptococcal glomerulonephritis) or those residing in a region with a high prevalence of GAS (Reference 95). In addition, age ranging from 5 to 15 years, winter months, enlarged anterior cervical lymph nodes (greater than 1 cm), and temperature between 101°F and 103°F are predictive factors for positive GAS throat cultures and scarlatiniform rash (References 85, 92). Laboratory confirmation should be performed in children who present with acute onset of sore throat with pharyngeal exudates or pain on swallowing and who possess or exhibit these predisposing factors.

The throat culture for diagnostic workup is the gold standard and is more cost-effective than RADT (References 90, 96). Neither test can differentiate between infection and carrier state; however, throat cultures are highly sensitive and specific in identifying GAS as well as other bacteria. The throat culture should thus be used in primary testing to confirm the presence of GAS. Even if RADT is employed initially, negative RADT, with its limited sensitivity, should always be confirmed with throat cultures in children and adolescents (References 81, 92). Situations in which RADT may be beneficial are when throat culture results are unavailable for more than 48 hours (i.e., RADT results are available in minutes) and when testing is performed in children who are highly likely to have positive throat cultures. Because RADT is very specific (95%–98%), a positive test is adequate for antibiotic initiation. Serologic testing for antistreptococcal antibody titers can validate true streptococcal infection (References 81,

95). However, positive titers occur 2–3 weeks after infection; hence, they are not valuable during the diagnostic process for acute GAS pharyngitis.

Complications caused by GAS pharyngitis consist of acute rheumatic fever, acute glomerulonephritis, streptococcal toxic shock syndrome, and scarlet fever. Some of these sequelae are serious and potentially life threatening (Reference 83). Other complications, particularly those of a purulent nature, include otitis media, sinusitis, peritonsillar and retropharyngeal abscesses, necrotizing fasciitis, and bacteremia.

Treatment

Antibiotic treatment is indicated for symptomatic GAS pharyngitis because it can progress to serious complications. In particular, antibiotic therapy eradicates certain GAS strains that can elicit an immune response, subsequently leading to acute rheumatic fever (Reference 90). Viral pharyngitis, in contrast, can self-resolve with or without adjunctive remedies for symptomatic relief. Laboratory confirmation of GAS as the etiologic agent during diagnostic workup is essential to appropriately managing the infected patient as well as ensuring judicious antimicrobial use (i.e., avoiding antibiotics in patients with viral infections).

Preventing the subsequent development of acute rheumatic fever is the primary goal for antibiotic treatment. Symptomatic recovery, eradication of GAS from the pharynx, prevention of suppurative and nonsuppurative complications, and prevention of transmission are other therapeutic goals. Symptom resolution generally occurs within 3–4 days but can occur as soon as 2 days with appropriate antibiotic therapy. To expedite clinical recovery, antibiotics should be initiated promptly within the first 2 days of infection, if possible (Reference 97). However, prevention of rheumatic fever requires antibiotic initiation within 9 days after illness onset (Reference 98). Eradication of GAS from the upper respiratory tract is an indicator of successful prevention of rheumatic fever. Prevention of glomerulonephritis through antibiotic use remains unclear (Reference 97). Although the risk of transmitting GAS pharyngitis peaks during acute infection, communicability decreases markedly after 24 hours of appropriate antibiotic therapy (References 83, 99).

Pharmacologic Therapy

Penicillin, available in oral and injectable formulations, is the treatment of choice for GAS pharyngitis because it is effective, safe, and relatively inexpensive (Table 1) (References 81, 83, 90). Injectable benzathine penicillin G is beneficial for children at enhanced risk of rheumatic fever, including those who live in crowded conditions or have a history of rheumatic heart disease. In addition, benzathine penicillin G is a prudent choice for children who are nonadherent to oral penicillin, which is a major contributing factor to treatment failure. Because one dose provides bactericidal levels for about 2 weeks, benzathine penicillin G is administered as a single intramuscular dose for the treatment of GAS pharyngitis (Reference 100). Benzathine penicillin G should be warmed to room temperature before intramuscular injection to minimize pain. The combination product containing benzathine penicillin G and procaine penicillin G can be considered to minimize discomfort (Reference 83).

Predominantly for young children, amoxicillin is a reasonable oral alternative to penicillin because of its enhanced palatability and activity against GAS. Other oral antibiotics are reserved for patients with penicillin allergies (Table 1). With their enhanced microbiologic and clinical cure rates in children, cephalosporins are excellent substitutes for those with mild penicillin allergies (References 101–103). However, first-generation cephalosporins are preferred because of their cost-effectiveness and because of concerns about antibiotic resistance with second- and third-generation cephalosporins (Reference 101).

Cephalosporins should be avoided in children with life-threatening immediate or type I hypersensitivity to β-lactams. Oral clindamycin and macrolides, including azithromycin, are appropriate options in these patients, but their selection for use should be based on local susceptibility patterns (Table 1). Because of their reported high resistance rates and failure to eradicate GAS, sulfonamides and tetracyclines should not be used for treating pharyngitis (Reference 83).

Empiric antibiotic initiation while waiting for confirmatory laboratory results remains controversial. The decision to initiate antibiotics empirically should be based on patient circumstances, although prevention of rheumatic fever allows antibiotic initiation as late as the ninth day of illness, when laboratory results should be available (References 94, 98). Antibiotics should be discontinued in the absence of positive throat cultures or RADT, except in patients with acute rheumatic fever who may initially have negative throat cultures. The duration of oral penicillin or amoxicillin therapy to achieve pharyngeal GAS eradication and thereby prevent acute rheumatic fever is 10 full days, even in the presence of clinical resolution. Shorter courses of oral therapy, with efficacy similar to a 10-day course of penicillin, are available for cefpodoxime, cefdinir, cefixime, cefadroxil, and azithromycin.

A posttreatment throat culture to confirm cure is recommended for patients and their domestic contacts, even if asymptomatic, who developed pharyngitis during an outbreak of acute rheumatic fever or poststreptococcal glomerulonephritis; have a history or are at high

risk of rheumatic fever; or have several family members in whom GAS infection has occurred (References 83, 104). More importantly, under these circumstances, asymptomatic household contacts with positive laboratory results should be treated with a standard course of antibiotic therapy.

Complications, including acute rheumatic fever, are unlikely to occur from pharyngitis caused by bacteria other than GAS; therefore, antimicrobial therapy is unnecessary in many of these situations, except for rare cases of acute pharyngitis caused by *C. diphtheria*, *N. gonorrhoeae*, and *A. haemolyticum*. In addition, antibiotics (usually for 5 days) may improve clinical response to non-group A streptococcal pharyngitis; hence, antibiotics may be considered in this situation (Reference 90). Pharmacologic and nonpharmacologic therapies for other causes of acute pharyngitis may be warranted, including activity restriction for EBV mononucleosis to prevent splenic rupture, acyclovir for HSV, and other antiviral agents for influenza.

Recurrent Infection and Pharyngeal Carriage

Recurrence of acute pharyngitis may occur in some children, particularly in those who are nonadherent to prescribed antibiotics, those who are streptococcal pharyngeal carriers with concurrent viral infection, those acquiring a new infection from GAS-infected close contacts, or those with a history of rheumatic fever. Streptococcal carriage occurs in 20% of asymptomatic school-aged children and may persist for months in the pharynx. Carriers can be identified by positive GAS laboratory tests between episodes of acute pharyngitis when carriers are asymptomatic or by serologic response to GAS extracellular antistreptolysin O antigen (even though titers are generally low) (Reference 83). Transmission of GAS to close contacts and development of suppurative complications are low in GAS carriers. However, eradication of GAS presents a therapeutic challenge (References 105, 106). Nonetheless, antibiotic therapy is indicated for GAS pharyngeal carriers only under special circumstances, including an outbreak of acute rheumatic fever, a case of poststreptococcal glomerulonephritis, or a family history of acute rheumatic fever (Reference 83).

A repeated course of antibiotics, using any of the therapeutic options other than the one prescribed initially, is indicated for those with a second incident of laboratory-confirmed pharyngitis. Intramuscular benzathine penicillin G is a practical selection for those with medication adherence issues. In addition, clindamycin and amoxicillin/clavulanate are effective for recurrent GAS pharyngitis, given their high eradication and clinical cure rates (Reference 107). These are reasonable options for patients with several recurrent episodes, which are likely caused by non-streptococci (i.e., viral) in GAS pharyngeal carriers. A combination of rifampin for the last 4 days of treatment with penicillin is an alternative for chronic streptococcal carriage (References 57, 83, 92). Tonsillectomy is not recommended if the goal of therapy is solely reduction in the episodes of GAS pharyngitis (Reference 92).

Adjunctive Therapy

Nonprescription remedies for sore throat, including lozenges and mouthwashes, provide few benefits (Reference 83). Similarly, antihistamines and decongestants offer minimal symptomatic relief. With their potential risks of adverse drug effects, these adjunctive therapies are not recommended for routine use in children and adolescents with URTIs. Acetaminophen or ibuprofen can be advantageous for its analgesic and antipyretic effects and thus can be considered an adjunct to antibiotic therapy (Reference 92).

Prevention

Secondary prevention of recurrent rheumatic fever using prophylactic antibiotics is recommended for individuals with a documented history of acute rheumatic fever or rheumatic heart disease (Reference 83). Penicillin, including penicillin G benzathine administered every 3–4 weeks, is recommended for secondary prophylaxis. Otherwise, sulfadiazine, sulfisoxazole, or macrolides can be substituted for patients with anaphylactic reactions to penicillin. Leukopenia associated with sulfonamides may occur after 2 weeks of prophylaxis and should be monitored.

Chemoprophylaxis should be initiated at the time of diagnosis and continued indefinitely for children with rheumatic heart disease. For individuals with rheumatic fever, antibiotic prophylaxis should be continued for at least 5 years, or until these individuals are 21 years old (whichever is longer). Although not well studied under controlled environments, tonsillectomy may be considered for patients with six or more GAS infections per year—or five or more episodes each year in 2 consecutive years (Reference 108).

Conclusions

Acute pharyngitis can be caused by viruses or bacteria. Discerning the clinical manifestations for each form of acute pharyngitis is imperative in identifying pediatric patients with GAS pharyngitis, an infection that can progress to serious complications including acute rheumatic fever. Patients with GAS pharyngitis are usually between 5 and 15 years of age; and acutely present with exudative sore throat, fever, and cervical lymphadenitis. Diagnosis should be confirmed with laboratory testing before initiating antibiotic therapy to ensure the appropriate use of these therapies.

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CHAPTER 37

Lower Respiratory Tract Infections

Kristin C. Klein, Pharm.D., FPPAG

Learning Objectives

1. List the goals of therapy for the treatment of bronchiolitis, pertussis, acute bronchitis, influenza, and community-acquired pneumonia.
2. Describe the role of palivizumab in the prevention of bronchiolitis.
3. Describe when postexposure prophylaxis would be beneficial for a child exposed to pertussis.
4. Describe situations in which the use of antivirals might be beneficial for the treatment of influenza in pediatric patients.
5. Formulate an appropriate antibiotic regimen for a pediatric patient with pertussis, community-acquired pneumonia, lung abscess, empyema, or necrotizing pneumonia on the basis of age, infecting organism, and severity of illness.

Abbreviations in This Chapter

AAP	American Academy of Pediatrics
CA-MRSA	Community-associated methicillin-resistant *Staphylococcus aureus*
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CYP	Cytochrome P450
LRTI	Lower respiratory tract infection
MIC	Minimum inhibitory concentration
MRSA	Methicillin-resistant *Staphylococcus aureus*
OTC	Over-the-counter
PCR	Polymerase chain reaction
PICU	Pediatric intensive care unit
PRSP	Penicillin-resistant *Streptococcus pneumoniae*
RSV	Respiratory syncytial virus
WHO	World Health Organization

Introduction

Lower respiratory tract infections (LRTIs) are a significant cause of morbidity and mortality in pediatric patients. Between 2006 and 2008, 25% of all hospitalizations in American children younger than 5 years were caused by an LRTI (Reference 1). This chapter will discuss the management of LRTIs commonly observed in pediatric patients.

Bronchiolitis

Bronchiolitis is the most common LRTI in infants younger than 12 months and is usually the result of a viral infection (Reference 2). Bronchiolitis is characterized by inflammation of the bronchioles and is often associated with wheezing (Reference 3). In addition to inflammation, bronchiolitis is associated with airway edema, epithelial lining necrosis, mucous production, and bronchospasm (Reference 4). Infection occurs after exposure to infected respiratory droplets. The incubation period is generally 2–8 days, but it may last up to 4 weeks in young infants (Reference 5).

Epidemiology

In the United States, bronchiolitis usually occurs during winter months (November through April). Many viruses have been implicated as causing bronchiolitis, but respiratory syncytial virus (RSV) has been most closely associated and is the causative organism in 80% to 100% of cases occurring during the winter months (References 4, 5).

It is estimated that more than 2 million children younger than 5 years require medical intervention each year in the United States because of bronchiolitis from RSV and that 3% of children are hospitalized for bronchiolitis during the first year of life (References 4, 6). Bronchiolitis is a significant cause of hospitalization, with an estimated annual cost to the health care system of $500 million (References 7, 8). By 2 years of age, almost 100% of children will contract RSV (Reference 9). Infection with RSV does not confer lifelong immunity. Reinfection with RSV can occur throughout a person's lifetime (Reference 3). An estimated 200–500 children die of RSV bronchiolitis annually in the United States, and about 80% of these deaths occur in infants younger than 12 months (Reference 10). In one study, an overall

mortality rate of 0.9% caused by RSV infection was reported, but the mortality rate for infants admitted to the pediatric intensive care unit (PICU) with RSV was significantly higher (4.4%) (Reference 11). All the infants who died had underlying medical conditions, such as chronic lung disease, cardiac abnormalities, chromosomal abnormalities, or immunodeficiency. None of the deaths occurred in previously healthy children.

Children who develop RSV bronchiolitis are also at higher risk of recurrent wheezing episodes throughout childhood and adolescence (References 12, 13). The link between wheezing and RSV bronchiolitis is not fully understood. It is theorized that children who are predisposed to developing asthma are more likely to have severe RSV disease. Alternatively, severe RSV infections may cause lung damage, making a child more susceptible to developing asthma later in life. In one study, children who developed RSV bronchiolitis before 1 year of age were followed until 18 years of age to determine whether recurrent wheezing or asthma persisted into early adulthood (Reference 12). Recurrent wheezing or asthma occurred in 39% of the RSV-infected group compared with 9% of the control group at 18 years of age, showing that this effect persists at least through late adolescence (Reference 12).

Etiology

In addition to RSV, viruses associated with bronchiolitis include rhinovirus, human metapneumovirus, human bocavirus, influenza A and B, adenovirus, and parainfluenza viruses (References 14, 15). Children at highest risk of developing severe RSV bronchiolitis include those with prematurity (especially younger than 35 weeks' gestation), chronic lung disease, bronchopulmonary dysplasia, or congenital heart disease (References 16, 17). Additional risk factors associated with contracting RSV include birth within 6 months of the RSV season, product of multiple births, attendance at day care, school-aged siblings, exposure to cigarette smoke, neuromuscular disease, and low socioeconomic status (References 5, 17).

Clinical Presentation

For most children, bronchiolitis initially presents with cold-like symptoms, such as low-grade fever, rhinorrhea, and cough (References 3, 17). Tachypnea, wheezing, retractions, and nasal flaring may also be present later in the disease course (References 3, 17). Bronchiolitis is generally a self-limited condition. Most children with bronchiolitis experience complete resolution of their symptoms within 8–15 days without needing medical intervention (Reference 17). Those who experience more severe disease might present with the additional symptoms of hypoxia, cyanosis, apnea, and respiratory distress (References 3, 17). Infants with more severe disease will likely require hospitalization, may require mechanical ventilation, and, in extreme cases, may require extracorporeal membrane oxygenation until the lung injury has improved.

Diagnosis

The American Academy of Pediatrics (AAP) recommends diagnosing bronchiolitis based on clinical presentation, a thorough history and physical examination, and investigation of known risk factors in a child presenting with probable bronchiolitis (Reference 3). Diagnosis of RSV bronchiolitis should also consider the time of year and the respiratory viruses circulating in the community. For example, RSV likely would not be considered the cause of a child's presenting with bronchiolitis during the summer months unless the virus was circulating through the local community. Infants presenting with probable bronchiolitis should be evaluated for risk factors for severe disease (e.g., history of premature birth, younger than 12 weeks, chronic lung disease, congenital heart defect, immunodeficiency) to help determine whether hospitalization is warranted. Other nonspecific indicators of infection, such as white blood cell count, are not clinically useful in diagnosing bronchiolitis. As with other viral infections, these values are likely to be within normal limits or only slightly elevated.

Viral cultures and antigen testing of nasopharyngeal swabs and chest radiography are of limited benefit in diagnosing bronchiolitis because their results do not help predict the severity of illness. The polymerase chain reaction (PCR) tests for many of the viruses that commonly cause bronchiolitis are now available commercially, which may allow faster, more reliable identification of these viruses.

Prevention

Palivizumab is a humanized monoclonal antibody specific for RSV. It is labeled for prevention of LRTIs from RSV in high-risk pediatric populations (Reference 18). Palivizumab is currently the only product licensed for the prevention of RSV infection in the United States.

Palivizumab is administered at a dose of 15 mg/kg intramuscularly every month during the RSV season. The RSV season generally occurs from late October or early November to late March or early April; however, prophylaxis should not be initiated until the local RSV season has begun. The season officially starts when the average RSV positivity rate is 10% or greater in the community for 2 consecutive weeks (Reference 19). The season ends when the community's positivity rate drops below 10% (Reference 19). Prophylaxis should continue until a child has received the maximum number

of doses recommended, even if the community positivity rate drops below 10%. Palivizumab is generally well tolerated. The most common adverse effects include fever and injection site reactions, such as pain, redness, or swelling (Reference 20).

The AAP recently updated its recommendations regarding the use of palivizumab for prevention of severe RSV infections. The AAP recommends palivizumab prophylaxis be considered for the following pediatric populations: infants born at younger than 32 weeks' gestation; infants and children younger than 24 months with chronic lung disease who required medical management of their chronic lung disease within 6 months of the start of RSV season; infants and children younger than 24 months with a "hemodynamically significant" congenital heart defect; and infants born between 32 weeks' and 34 weeks 6 days' gestation with additional risk factors (Reference 21). Infants born at younger than 29 weeks' gestation may benefit from palivizumab prophylaxis during RSV season through the first 12 months of age. Those born between 29 and 32 weeks' gestation may benefit from prophylaxis during RSV season through the first 6 months of life. Refer to Table 1 for more information regarding the use of palivizumab for prophylaxis of RSV bronchiolitis.

Palivizumab serum concentrations remain above the concentration necessary to suppress viral replication for greater than 30 days after several doses, resulting in sustained RSV protection well beyond administration of a fifth dose of palivizumab (References 20, 21). This led the AAP to recommend a limit to the number of doses of palivizumab that at-risk infants should receive. For infants born between 32 weeks and 34 weeks 6 days who qualify for palivizumab administration, the AAP recommends monthly palivizumab for three doses or until 3 months of age, whichever comes first (Reference 21). All other high-risk infants and children may receive a maximum of five doses of palivizumab during the RSV season (Reference 21).

The updated AAP maximum dose limitation has generated a fair amount of controversy. If palivizumab administration begins in October, then the last dose of palivizumab a child is eligible to receive would occur in February, potentially 4–6 weeks before the end of the RSV season. Most insurance companies cover only the cost of palivizumab doses that meet the AAP criteria for administration. As a result, if the recommended number of doses of palivizumab is exceeded, then either the child's caregivers will be financially responsible for the costs associated with the additional doses or the health care facility will be required to cover the cost. The average wholesale price for a 100-mg vial of palivizumab is around $2,200, which can result in a substantial financial loss to a health care facility if the facility initiates early prophylaxis (Reference 22).

Table 1. Indications for Palivizumab Prophylaxis (Reference 21)

Indication	Maximum Number of Doses
Premature infants < 32 weeks' gestation	5
Premature infants 32 weeks' to 34 weeks 6 days' gestation[a]	3
Infants < 24 months with chronic lung disease[b]	5
Infants < 24 months with certain congenital heart diseases[c]	5

[a]Indicated if the child is younger than 3 months at the start of the RSV season or if the child has the additional risk factor of attending day care or living in a home with other children younger than 5 years.
[b]Indicated if the child requires oxygen or pharmacologic treatment of lung disease within 6 months of RSV season.
[c]Indicated if the child has a "hemodynamically significant" cardiac lesion (e.g., cyanotic heart disease, moderate or severe pulmonary hypertension, receiving therapy for congestive heart failure).
RSV = respiratory syncytial virus.

Treatment

The goals of therapy for bronchiolitis are to maintain oxygenation, maintain adequate hydration, and reduce fever. The treatment of bronchiolitis is primarily supportive. Supplemental oxygen and intravenous fluids may be necessary to limit symptoms and avoid dehydration. Both nonpharmacologic and pharmacologic therapies for bronchiolitis will be discussed in this chapter.

Nonpharmacologic Therapy

Healthy children generally exhibit oxygen saturations above 95% (Reference 3). Children with bronchiolitis may exhibit a decrease in oxygen saturations because of airway edema, excessive mucous production, and bronchospasm. For this reason, the AAP recommends children with signs or symptoms consistent with bronchiolitis receive supplemental oxygen once their O_2 saturations decrease below 90% (Reference 3).

Chest physiotherapy, the process of using percussion or vibration to clear the airways, has been used in other pulmonary diseases, like cystic fibrosis. A study evaluating the use of chest physiotherapy compared with nasal suctioning in infants with bronchiolitis found no significant differences in recovery time between the two groups (Reference 23). Other studies have also failed to show a significant improvement in children

with bronchiolitis treated with chest physiotherapy. As a result, the AAP does not recommend the routine use of physiotherapy as a treatment option for infants with bronchiolitis (Reference 3).

Heliox therapy, a blend of helium and oxygen, is an intervention that was recently evaluated for bronchiolitis. In a recent review, heliox was associated with an improvement in respiratory scores, but it was not associated with significant improvements in the need for intubation and mechanical ventilation or in the length of PICU stay (Reference 24). Heliox is unlikely to benefit infants with bronchiolitis.

Pharmacologic Therapy

Both α-adrenergic (e.g., racemic epinephrine) and β-adrenergic (e.g., albuterol) bronchodilators have been used in the management of bronchiolitis. A 2010 Cochrane review evaluated 28 studies to determine the effectiveness of bronchodilators for outcomes such as oxygen saturation, clinical improvement, and length of hospital stay (Reference 25). For children who received bronchodilators as outpatients, there was no significant reduction in hospitalization rates (Reference 25). For children who received bronchodilators as inpatients, there was no significant reduction in length of hospital stay (Reference 25). Bronchodilators also failed to show a significant improvement in oxygen saturation (Reference 25). However, children who received bronchodilators did exhibit a small, although nonsignificant, improvement in clinical scores (Reference 25). The AAP does not recommend the routine use of bronchodilators for children with bronchiolitis (Reference 3). The AAP does, however, acknowledge that some children may exhibit clinical improvement after receipt of bronchodilators, so a trial of bronchodilators may be attempted (Reference 3). However, children receiving bronchodilators should be closely monitored, and therapy should be discontinued if no improvement is observed.

Corticosteroids such as dexamethasone and methylprednisolone have been theorized to reduce inflammation associated with bronchiolitis. A 2010 Cochrane review evaluated the use of both inhaled and systemic corticosteroids for bronchiolitis for reduction in hospitalization and length of hospital stay (Reference 26). Similar to other pharmacologic interventions discussed previously, corticosteroids did not show a significant reduction in hospitalizations, nor did they show a significant decrease in length of hospital stay (Reference 26). The AAP does not recommend the routine use of corticosteroids in children with bronchiolitis, although children with asthma who develop bronchiolitis may benefit from corticosteroids (Reference 3).

The use of nebulized hypertonic saline (3% to 12%) was identified as a treatment modality for clearing mucous plugs in individuals with cystic fibrosis in the mid-2000s. In recent years, its use has been studied in bronchiolitis. A Cochrane review found that children who received 3% hypertonic saline had significantly shorter lengths of hospital stay (mean of 1.16 fewer hospital days, $p<0.00001$) and significantly lower clinical severity scores during the first 3 days of therapy (lower scores indicate less severe response to disease) (Reference 27). The authors concluded that the use of nebulized hypertonic saline 3% may be beneficial in reducing length of hospital stay and severity scores for infants with bronchiolitis. A major criticism of this review is that bronchodilators were used in conjunction with hypertonic saline for many of the studies that were included, making it difficult to differentiate the effects of the two agents used (Reference 28).

Ribavirin is a nucleoside analog with activity against RSV. Inhaled ribavirin has been used for decades as the primary treatment of RSV bronchiolitis; however, its use has decreased dramatically during the past 10–15 years. Many published clinical trials have shown that inhaled ribavirin does not improve clinical outcomes, such as time on the ventilator, length of stay in the intensive care unit, or hospital length of stay (References 29–31). Inhaled ribavirin requires administration by a special nebulizer (SPAG-2 [small-particle aerosol generator]) for a minimum of 12–18 hours (Reference 32). It has teratogenic potential in animal models and is a pregnancy risk category X (Reference 32). As a result, women of childbearing age, including female nurses and the mothers of infected children, should be counseled regarding the teratogenic potential, and pregnant women should not be allowed in a recipient's room during administration. Although oral ribavirin is contraindicated in male partners of pregnant women, the risk of teratogenicity after exposure of the male partner to inhaled ribavirin is unknown. Inhaled ribavirin has been associated with bronchospasm, hypotension, bradycardia, and hemolytic anemia (Reference 32). The use of inhaled ribavirin may also cause considerable anxiety to the child because of isolation from other children or a pregnant mother and feelings of claustrophobia if the child is placed in a tented crib to receive the aerosol. Aerosolized ribavirin may also stick to contact lenses (Reference 32), so contact lens wearers should avoid entering the room of a child receiving ribavirin. If a contact lens wearer must enter the room of a child receiving ribavirin, he or she should wear protective goggles. Because of ribavirin's adverse effects, administration difficulties, and unproven benefit, the AAP does not recommend routine ribavirin administration to infants and children with bronchiolitis (Reference 3).

Antibiotics have been used in children with bronchiolitis; however, their use does not result in significant clinical improvement (Reference 33). Bronchiolitis is primarily the result of a viral infection. As such, antibiotics should be reserved for children with a concomitant bacterial infection (Reference 3).

Leukotriene antagonists have been used in asthma for more than a decade, and recently, the leukotriene antagonist montelukast was evaluated for use in bronchiolitis. One study showed significantly shorter hospital lengths of stay in infants and children 24 months and younger who were hospitalized for bronchiolitis and received montelukast compared with placebo (Reference 34). Another study showed a significant decrease in wheezing 12 months after the use of montelukast in infants and children 6–24 months of age who received montelukast for 3 months after hospitalization for bronchiolitis (Reference 35). These two studies included less than 250 pediatric subjects. As such, more studies regarding the utility of leukotriene antagonists for bronchiolitis are warranted.

Conclusions

Many pharmacologic and nonpharmacologic therapies have not shown efficacy in relieving symptoms or improving clinical outcomes in children with bronchiolitis. The AAP has not revised its recommendations regarding the medical management of children with bronchiolitis since 2006, so newer therapies such as nebulized hypertonic saline and leukotriene antagonists are not presently recommended but may be of benefit. Because smoking exposure is a modifiable risk factor for bronchiolitis, parents and caregivers should be counseled to quit smoking. If that is not possible, they should be counseled not to smoke in the home, car, or other locations where their children are present. Families should also be counseled regarding proper hand hygiene, including washing hands before and after contact with a sick child.

Pertussis

Pertussis, commonly known as whooping cough, is a respiratory tract infection caused by the gram-negative organism *Bordetella pertussis*. Pertussis is highly contagious. Infection occurs through exposure to contaminated respiratory droplets after close contact with an infected individual. The incubation period for pertussis is usually 7–10 days after exposure but may last as long as 21 days (Reference 36). Infected individuals are most contagious during the first 1–2 weeks of infection (known as the catarrhal phase) and within 2 weeks of the onset of cough (Reference 36).

Epidemiology

Before a pertussis vaccine became available in the 1940s, more than 200,000 people became infected with *B. pertussis* annually in the United States (Reference 37). Pertussis infections decreased dramatically after routine use of the pertussis vaccine; however, the number of pertussis infections reported to the Centers for Disease Control and Prevention (CDC) has been increasing since the 1980s, reaching a high of 8.88 cases per 100,000 people in 2004 (References 37, 38). Pertussis infection rates declined after the 2004 peak; however, the incidence is again on the rise, with a new high of 8.97 cases per 100,000 people reported in 2010 (Reference 39).

Before the availability of a vaccine, pertussis was a disease primarily found in school-aged children. Since the early 2000s, the incidence of pertussis has increased in infants (younger than 12 months), adolescents, and adults (Reference 37). The highest incidence of pertussis during 2009 occurred in infants, especially those younger than 6 months (126.9 per 100,000); however, adolescents and adults accounted for almost 50% of pertussis cases reported to the CDC in 2009 (Reference 38).

During the first half of 2010, a significant increase in the number of individuals infected with pertussis was documented in the state of California. From January through June, more than 1300 pertussis cases were reported to the California Department of Public Health, representing a 418% increase from the 258 cases reported during the same period in 2009 (Reference 40). During the California outbreak, the highest incidence of pertussis occurred in infants younger than 12 months (38.5 cases per 100,000 people), with infants younger than 6 months representing 89% of the cases reported (Reference 40). Five deaths were reported, all of which occurred in Hispanic infants younger than 2 months (Reference 40).

For several reasons, a shift in disease burden away from school-aged children has been observed. First, an improvement in the ability to reliably diagnose pertussis and an increase in its awareness, both in the lay public and in health care practitioners, likely contributed to an increase in the diagnosis of pertussis in other populations (Reference 41). Additional factors that have been suggested as contributors to the shift in disease burden include a decrease in vaccine coverage (i.e., fewer people receiving the vaccine) and waning of vaccine-induced immunity over time (Reference 41). Unvaccinated or under-vaccinated adolescents and adults often serve as the reservoir for infants infected with *B. pertussis*.

The most common complication of pertussis is pneumonia. About 5% of all individuals with pertussis whose cases were reported to the CDC between 1997 and 2000 developed pneumonia (Reference 37). The incidence of pneumonia in infants younger than 6 months was 11.8%, more than twice the rate of pneumonia for

all individuals during that time (Reference 37). Other pulmonary complications that have been described with pertussis include cyanosis, apnea, pulmonary hypertension, hypoxia, and need for oxygen supplementation or mechanical ventilation (References 37, 42, 43). Other complications reported in infants include poor feeding, anorexia, seizures, and encephalopathy, possibly because of hypoxia caused by coughing (References 37, 42).

Infants are at the highest risk of death from pertussis infection, especially those who are too young to be vaccinated (or completely vaccinated) against pertussis. During the 1980s, 77 deaths were reported to the CDC, 61 (79%) of which occurred in infants younger than 12 months (Reference 44). Forty-nine (80%) of the infant deaths occurred in infants younger than 4 months (Reference 44). Between 1990 and 1999, 103 deaths from pertussis were reported to the CDC, 90% of which occurred in infants (Reference 44). Eighty-four of the infants who died were younger than 4 months, representing 90% of the infant deaths (Reference 44). Hispanic ethnicity has also been identified as a risk factor for death from pertussis (References 42, 43).

Adolescents and adults are much less likely to exhibit significant morbidity because of pertussis. Pertussis also has a much lower mortality rate in adolescents and adults, occurring in only 0.1% of infected individuals in these age ranges (Reference 45). Pneumonia has been reported in 2% to 9% of adolescents and adults infected with pertussis, with the highest rates reported in older individuals (Reference 45). The most common complications of pertussis reported in adolescents and adults include loss of bladder control, rib fractures, pneumothoraces, anorexia, and weight loss (References 37, 45, 46). Rib fracture is more likely to occur in individuals with profound paroxysmal coughing and in those with osteoporosis (Reference 45). Intracranial hemorrhages have also been reported but are more common in individuals who receive anticoagulants (Reference 45). Seizures and encephalopathy have also been reported in this population, but they occur in less than 1% of those infected (Reference 45).

Etiology

Disease from pertussis is primarily caused by toxin production by the organism, which causes impaired mucociliary function and lung inflammation (Reference 47). This leads to an inability to clear respiratory secretions and the associated cough.

Clinical Presentation

Pertussis infection has three phases: catarrhal, paroxysmal, and convalescent. The catarrhal phase usually lasts 1–2 weeks, and symptoms generally mimic those of the common cold (e.g., rhinorrhea, sneezing, cough, and low-grade fever) (Reference 37). Infected individuals are most likely to be contagious during this phase of the disease. The next phase, the paroxysmal phase, may last anywhere between 1 and 6 weeks and is when the classic paroxysmal cough, followed by an inspiratory whoop, occurs (Reference 37). The cough is characterized by a burst of persistent, rapid coughs (known as paroxysms) and the accompanying whoop that is caused by a narrowed glottis during a prolonged inspiratory period. Children, especially young infants, can become cyanotic and may appear visually ill during these episodes (Reference 37). The paroxysms are more frequent at night and increase in frequency throughout this phase of the disease. Posttussive emesis is also common during this phase, especially in adolescents (Reference 48). The convalescent, or recovery, phase, during which symptoms slowly improve as the paroxysms begin to resolve, may last weeks to months (Reference 37). Unvaccinated infants and children are more likely to have severe disease. Older children who have been vaccinated, adolescents, and adults typically have less severe disease and may not present with the classic symptoms of pertussis, although they often present with a nagging cough that has persisted for several weeks (References 37, 48).

Diagnosis

The diagnosis of pertussis is often made using a combination of clinical presentation and microbiologic tests. Pertussis should be highly suspected in any child or adolescent who presents with a cough of greater than 2 weeks' duration (Reference 48). White blood cell counts are often elevated during pertussis and show lymphocyte predominance on a differential diagnosis (References 37, 48).

Several laboratory tests may be used to confirm the presence of *B. pertussis*. Bacterial culture is considered the gold standard for diagnosing pertussis; however, isolating *B. pertussis* by culture is often difficult because it is a fastidious organism. Bacterial cultures are much less sensitive over time. Once an infected individual has been symptomatic for 3 weeks, bacterial culture detects *B. pertussis* in only 1% to 3% of cases (Reference 49). Polymerase chain reaction is a more sensitive testing method, especially if the individual presents later in the disease course (References 37, 48, 49). Polymerase chain reaction also has the advantage of a rapid turnaround time because it does not measure the presence of living organisms. For children or adolescents who present late in the disease course, measuring antibody levels to pertussis antigens may be useful in confirming infection. Serology (or antibody) testing can be difficult to interpret in vaccinated individuals because positive serologies confirm only exposure to pertussis antigens. As a result, serologies should not be used routinely to confirm the diagnosis of pertussis (Reference 37).

Prevention

The primary mode for preventing the spread of pertussis is through vaccination of susceptible individuals against *B. pertussis*, especially those who may be exposed to infants who are not fully vaccinated. Several vaccines are available to protect against pertussis. Confusion regarding the various acronyms used to discuss the available pertussis vaccines is common, so it is important for health care practitioners to understand the differences and indications for each vaccine. Further information regarding the pertussis-containing vaccines may be found in the Pediatric Vaccines chapter.

Treatment

The primary goal of treatment for pertussis is to reduce transmission to infants and children at high risk of significant morbidity or mortality, such as infants younger than 4 months and children who are immunocompromised. Antimicrobial therapy initiated during the catarrhal phase of pertussis can hasten recovery from the disease. Once a cough has developed, antimicrobial therapy will not contribute to symptomatic improvement, but it can limit the spread of disease to susceptible individuals (Reference 36). Macrolide antibiotics are the treatment of choice for pertussis.

Erythromycin is the oldest macrolide antibiotic on the market in the United States and has, historically, been used first line in the treatment of pertussis. Erythromycin is the only macrolide antibiotic labeled for use in infants younger than 6 months; however, when used in young infants, it has been associated with an increased risk of infantile hypertrophic pyloric stenosis (References 36, 50). This risk appears to be highest during the first 2 weeks of life and when given for 14 or more days (Reference 50). Erythromycin, which should be administered four times/day, has a high rate of gastrointestinal adverse effects, including abdominal cramping, nausea, vomiting, and diarrhea. Erythromycin is a potent inhibitor of the cytochrome P450 (CYP) 3A subclass with many drug-drug interactions (Reference 51). Although QT prolongation has been associated with all the macrolide antibiotics, erythromycin has the highest risk of QT prolongation (Reference 51). Because of these factors, erythromycin is no longer the macrolide antibiotic of choice for pertussis.

Azithromycin is generally better tolerated than the other macrolide antibiotics. Azithromycin has the advantages of once-daily dosing and a shortened length of therapy of only 5 days. The most common adverse effects include gastrointestinal upset, diarrhea, vomiting, headache, and dizziness. Azithromycin is a less potent inhibitor of the CYP system than the other macrolide antibiotics and has fewer drug-drug interactions. Although pyloric stenosis in young infants has been reported with azithromycin, the incidence appears to be much lower than that associated with erythromycin (Reference 36). For these reasons, azithromycin is often used as the first-line agent for pertussis, even in infants younger than 6 months. Infants younger than 6 months receiving azithromycin therapy should be closely monitored for signs of pyloric stenosis (References 50, 51).

Clarithromycin is structurally similar to erythromycin. As such, it has similar effects on the CYP system and similar drug-drug interactions (Reference 51). Like erythromycin, clarithromycin is associated with substantial gastrointestinal adverse effects. It has the advantage over erythromycin of requiring only twice-daily dosing and a shorter therapy (7 days with clarithromycin vs. 14 days for erythromycin); however, it must be administered more frequently and for a longer duration than azithromycin. For these reasons, its use is limited in children.

For children or adolescents allergic to or intolerant of macrolide antibiotics, trimethoprim/sulfamethoxazole (TMP/SMX) may be used as an alternative (Reference 51). Infants younger than 2 months should not receive TMP/SMX unless the benefits of therapy outweigh the risks of hyperbilirubinemia and kernicterus that can result from the displacement of bilirubin from its protein-binding site. Information regarding the dose and duration of antibiotics for pertussis treatment is available in Table 2.

Postexposure Prophylaxis

Pertussis is a highly contagious, infectious disease. Up to 80% of people who have close contact with an infected person also contract pertussis; as a result, preventive antibiotics should be considered in certain situations (Reference 51). Close contact is defined in several ways. The CDC considers a close contact anyone who has face-to-face contact within 3 ft of an infected person (Reference 51). Anyone who has been exposed to an infected person's oral, nasal, or respiratory secretions (e.g., nurse, parent, day care provider) also qualifies as a close contact (Reference 51). Anyone who shares a confined space (e.g., car, bed, crib) with an infected person for at least 1 hour also qualifies as a close contact (Reference 51). If a household contact of an infected person develops a cough, he or she should receive a course of antibiotics for pertussis (Reference 51). If someone develops pertussis in a household with an infant younger than 12 months or a pregnant woman in her third trimester, all members of the household should receive preventive antibiotics (Reference 51). Preventive antibiotics may also be considered in close contacts at high risk of developing severe disease or complications from pertussis, such as children who are immunocompromised or who have chronic lung disease (Reference 51). Preventive antibiotics may be considered in other individuals who have had

Table 2. Antibiotics for Pertussis: Dosing and Duration of Therapy (Reference 51)

Antibiotic	Dose for Infants ≤ 5 Months	Dose for Infants/Children ≥ 6 Months	Dose for Adolescents/Adults	Therapy Duration (days)
Azithromycin	10 mg/kg/day	10 mg/kg on day 1; then 5 mg/kg/day on days 2–5	500 mg on day 1; then 250 mg/day on days 2–5	5
Clarithromycin[a]	7.5 mg/kg/dose BID	7.5 mg/kg/dose BID	500 mg BID	7
Erythromycin[a]	10 mg/kg/dose QID	10 mg/kg/dose QID	500 mg QID	14
TMP/SMX[b,c,d]	4 mg/kg/dose BID	4 mg/kg/dose BID	160 mg (1 double-strength tablet) BID	14

[a]Not recommended for infants younger than 1 month.
[b]Alternative agent for infants, children, or adolescents with an allergy or intolerance to macrolide antibiotics.
[c]Dosing is based on the trimethoprim component.
[d]Not recommended for infants younger than 2 months.
BID = twice daily; QID = four times/day; TMP/SMX = trimethoprim/sulfamethoxazole.

close contact with an infected person, but the benefits of therapy should be weighed against the risks of adverse effects before therapy is initiated. Antimicrobial therapy and duration of antimicrobials used for postexposure prophylaxis are the same as those used to treat pertussis.

Conclusions

Anyone with a cough lasting more than 2 weeks should be presumed to have pertussis until proven otherwise. Macrolide antibiotics, especially azithromycin, are the mainstay of treatment for pertussis. Therapy duration ranges from 5 to 14 days, depending on the antibiotic selected. Preventing pertussis transmission to at-risk populations is the most important step in treating pertussis. Parents and caregivers should be encouraged to have their children vaccinated against pertussis on time and according to schedule. If a household contact of an infant younger than 12 months or a pregnant woman in her third trimester contracts pertussis, then all members of the household should receive preventive antibiotics.

Acute Bronchitis

Acute bronchitis is a self-limited respiratory tract infection characterized by a cough lasting no more than 3 weeks (Reference 52). Acute bronchitis is usually triggered by a viral infection and is associated with inflammation of the bronchioles, airway hyperresponsiveness, and mucous production (Reference 53).

Epidemiology

Between 2001 and 2002 in the United States, cough was the most common symptom cited for seeking care in the ambulatory care setting, accounting for 4.3% of all outpatient visits by children and adults (Reference 54). Although acute bronchitis is largely caused by a viral infection, up to 80% of individuals with acute bronchitis inappropriately receive antibiotic therapy (Reference 52).

Etiology

Acute bronchitis is usually the result of infection from respiratory viruses, such as influenza A and B, parainfluenza, and RSV; however, cultures are rarely performed at the time of diagnosis (Reference 52). Although *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *B. pertussis* have also been associated with bronchitis, bacterial causes have been implicated in less than 10% of those with a diagnosis of bronchitis (Reference 52).

Clinical Presentation

Children who present with acute bronchitis typically have a cough with or without phlegm production. Because acute bronchitis is predominantly caused by respiratory viruses, its symptoms are often difficult to distinguish from those of the common cold. Acute bronchitis is a self-limited condition that should resolve within 3 weeks (Reference 52). A child who presents with a cough lasting more than 3 weeks should be evaluated for other conditions (e.g., pertussis).

Diagnosis

In making a diagnosis of acute bronchitis, other explanations for the cough need to be evaluated and excluded (Reference 52). A child with a cold may present with a cough; however, other symptoms, such as rhinorrhea and congestion, are often present (Reference 55). Symptoms of a cold also usually resolve within 7–10 days. A child presenting with pneumonia usually has

additional signs or symptoms, such as fever, tachycardia, tachypnea, or diminished breath sounds on auscultation, which rule out acute bronchitis as the cause of the cough (References 52, 55). A child with a history of asthma who presents with a cough should be evaluated for an acute asthma exacerbation. Once other possible explanations for a cough have been excluded, the diagnosis of acute bronchitis can be made (Reference 52). Viral and bacterial cultures should not be performed routinely in children with the presumed diagnosis of acute bronchitis (Reference 52).

Treatment

The primary treatment goal for acute bronchitis is to keep the child comfortable by ameliorating symptoms until the infection subsides. For most individuals with acute bronchitis, antibiotic therapy has limited benefit, if any. The American College of Chest Physicians does not recommend antibiotic therapy for individuals with the presumptive diagnosis of acute bronchitis (Reference 52). The overuse of antibiotics for conditions including acute bronchitis led to a campaign by the CDC called "Get Smart: Know When Antibiotics Work," designed to educate the public and health care practitioners regarding the appropriate use of antibiotics. For more information about the Get Smart campaign, refer to the campaign Web page (www.cdc.gov/getsmart/index.html).

Medications attempting to alleviate the symptoms associated with acute bronchitis have largely proven ineffective and may cause more harm than good in children. Antitussive agents, such as dextromethorphan or codeine, have shown some limited efficacy in adults but should not be used in children (References 52, 55, 56). These agents have not shown efficacy in children; moreover, they have been associated with unintentional overdoses (Reference 56). Infants and young children are also at increased risk of adverse effects from codeine because of immature hepatic function. The performance of the glucuronidation pathway, which is necessary to metabolize codeine, is highly variable in children younger than 10 years (References 56, 57). Decongestants and other cough or cold products should also be avoided in children, especially those younger than 4 years. In January 2008, the U.S. Food and Drug Administration (FDA) issued a Public Health Advisory stating that over-the-counter (OTC) cough and cold products should not be used in children younger than 2 years because of serious adverse effects reported in this population (Reference 58). Later that year, members of the Consumer Healthcare Products Association voluntarily agreed to change the package labeling of pediatric OTC cough and cold products to state that they should not be used in children younger than 4 years (References 58, 59). An alternative to OTC cough products, honey, when administered before bedtime to a child with an acute cough, has shown some success in decreasing the frequency and severity of cough and in improving the sleep of both the child and the parent (Reference 60). Honey should not be given to infants younger than 12 months, however, because of the risk of developing infant botulism.

Conclusions

Acute bronchitis is generally a self-limited condition that resolves on its own within 3 weeks of symptom development. Other possible explanations for cough (e.g., asthma, common cold, pneumonia) should be ruled out before a diagnosis of acute bronchitis is made. Antibiotic therapy is not warranted for children with acute bronchitis. Over-the-counter cough and cold products are not useful in children and are considered unsafe in children younger than 4 years. Parents and caregivers should be counseled that acute bronchitis is the result of a viral infection and that antibiotic therapy will not help relieve their child's symptoms.

Influenza

Influenza is transmitted through close contact with infected respiratory droplets. Infection usually occurs within 3–4 days of exposure (Reference 61). Infected individuals may remain symptomatic for up to 7 days (References 61, 62). Children who contract influenza may shed virus for 10 or more days (Reference 61). School-aged children have the highest attack rate and serve as the primary source of infection during influenza outbreaks (Reference 62). Influenza follows a seasonal pattern and typically occurs during the winter months.

Epidemiology

During 2009, more than 350 pediatric deaths were reported to the CDC, 81% of which were caused by the novel influenza A H1N1 strain (Reference 38). Children who died of influenza caused by this strain were older than those who died of a seasonal strain of influenza during the same year (9.3 years vs. 7.5 years) (Reference 38). Children who died secondary to novel H1N1 influenza infection were also more likely to have a comorbid condition than those who died secondary to seasonal influenza during 2009.

Children younger than 2 years and those with comorbid conditions, such as asthma or immunosuppression, are at highest risk of secondary complications from influenza (Reference 38). Children with a history of asthma and those younger than 5 years have a higher risk of developing pneumonia after infection with influenza (Reference 61). Children with influenza-associated pneumonia are at higher risk of admission

to an intensive care unit, respiratory failure, and death. Other complications of influenza infection in children include febrile seizures, myocarditis, pericarditis, encephalopathy, and Reye syndrome (Reference 61). Reye syndrome has been described in children younger than 18 years who were infected with influenza or varicella and who received aspirin therapy (Reference 62).

Etiology

Most influenza infections worldwide are caused by influenza A or B (Reference 63). Influenza A causes moderate to severe disease in individuals of all ages (Reference 62). Influenza A infects humans, birds, or other animals. Influenza B typically causes milder disease, primarily affects children, and infects only humans (Reference 62). Over time, gene mutations in the surface proteins of influenza result in subtle changes to the influenza subtypes, which circulate worldwide; this is known as antigenic drift (Reference 63). These drifts can result in community epidemics and require annual changes to the influenza A and B subtypes contained within the influenza vaccine. Another type of gene mutation, known as antigenic shift, occurs only in influenza A viruses and results in dramatic changes in the hemagglutinin or neuraminidase surface proteins of the virus (Reference 63). This results in a new viral strain that can lead to a pandemic if the virus is able to sustain person-to-person transmission. This occurred in 2009 with the novel influenza A H1N1 pandemic, in which it was estimated that 60 million individuals contracted this strain in the United States (Reference 62). This resulted in more than 275,000 hospitalizations and 12,500 deaths in both children and adults (Reference 62).

Clinical Presentation

The most common symptoms associated with influenza are fever, myalgias, sore throat, cough, rhinorrhea, and general malaise (Reference 61). Children infected with influenza may also present with otitis media, nausea, and vomiting. Children younger than 5 years are less likely to present with the classic symptoms of fever or cough (Reference 61). Signs and symptoms of influenza generally resolve within 3–7 days in uncomplicated cases.

Diagnosis

Diagnosis of influenza in the outpatient setting may be made on the basis of clinical presentation and knowledge of the respiratory viruses circulating in the community. Clinical diagnosis is nonspecific and may be of limited benefit because many respiratory viruses present with similar signs and symptoms. Microbiologic testing to confirm the diagnosis of influenza is useful to guide therapy. Microbiologic tests for influenza include viral culture, antigen testing, and PCR. The most common microbiologic tests used to detect influenza in the community are the rapid diagnostic tests, which can detect the presence of influenza from a nasopharyngeal swab within 15–30 minutes (Reference 64). Many of the rapid diagnostic tests can be used in any outpatient setting, making them convenient to use in a physician's office. The rapid diagnostic tests are immunoassays, which have a high degree of specificity (up to 95%) but a sensitivity of only 50% to 70% compared with viral culture or PCR (Reference 64). As a result, there is a higher possibility of yielding a false-negative result, especially when community rates of influenza are high (Reference 65). During community outbreaks of influenza, negative rapid diagnostic tests should be confirmed with a viral culture. False-negative results can be minimized by performing the rapid diagnostic test early in the course of illness (within 4–5 days) (Reference 65).

Prevention

Vaccination of all individuals older than 6 months, including adults, against influenza is the most effective way to prevent transmission of the disease. Parents, caregivers, and children should also be instructed to wash their hands frequently to prevent the spread of disease. Refer to the Pediatric Vaccines chapter for a more detailed discussion of the influenza vaccines.

Treatment

The goals of therapy for treating influenza in children are to alleviate the associated symptoms and prevent the spread of infection. Analgesic antipyretics such as acetaminophen are useful for managing fever and myalgias associated with influenza. Antiviral agents may also be beneficial in reducing the duration of symptoms in some children.

Two classes of antivirals have activity against influenza: the Adamantanes and the neuraminidase inhibitors. The Adamantanes (amantadine and rimantadine) do not have activity against influenza B, but until recently, they did exhibit activity against influenza A (Reference 61). Influenza resistance to the Adamantanes has been increasing for the past 5–10 years. During the 2009–2010 influenza season, 100% of the seasonal influenza A H3N2 viruses were resistant to the Adamantanes, whereas 99.8% of the pandemic influenza A H1N1 viruses tested were resistant to them (Reference 66). For this reason, the use of Adamantanes is not appropriate for the treatment or prevention of influenza infections.

The neuraminidase inhibitors (oseltamivir and zanamivir) have good activity against both influenza A and B, although influenza A resistance to oseltamivir has been documented. During the 2009–2010 influenza season, only 1.1% of the pandemic influenza A H1N1 viruses tested showed resistance to oseltamivir (Reference 66). None of the seasonal influenza A H3N2 or influenza B viruses showed oseltamivir resistance. All the viruses tested during the 2009–2010 season showed sensitivity to zanamivir, including those resistant to oseltamivir. The neuraminidase inhibitors are the agents of choice for the treatment and prevention of influenza in children.

Many children with suspected influenza infections who present with minor febrile illnesses will not require antiviral therapy. The use of oseltamivir in children 1–3 years of age reduced the duration of influenza symptoms to a median of 3.5 days when therapy was initiated within 24 hours of symptom onset (Reference 67). Because antiviral therapy may shorten the duration of influenza symptoms by only about 1 day on average, the decision to initiate antiviral therapy should consider the respiratory viruses circulating in the community, the individual's risk of developing complications of influenza infection, the severity of the individual's disease, and the duration of symptoms. The CDC recommends outpatient antiviral therapy be considered for previously healthy, symptomatic individuals who are at low risk of serious sequelae from influenza if therapy can be initiated within 48 hours of symptom onset (Reference 61). Once the decision to initiate therapy has been made, the antiviral should be continued for 5 days (Reference 61).

Individuals who are at highest risk of serious complications from influenza infection should receive antiviral therapy as early as possible after symptom onset, ideally within 48 hours (Reference 61). This includes all children younger than 2 years; children with other comorbid conditions (e.g., asthma, sickle cell disease, diabetes, seizure disorders, mental retardation, HIV [human immunodeficiency virus]); children 18 years and younger receiving chronic aspirin therapy; American Indians or Native Americans; and children who are residents of chronic care facilities. Early initiation of antiviral therapy for influenza may also reduce the risk of serious complications, such as influenza-associated pneumonia or death. Children who have severe, progressive disease or who have been hospitalized because of influenza should also receive antiviral therapy (Reference 61). A longer therapy duration may be warranted for critically ill children who have been admitted to the hospital or for immunocompromised children (Reference 61).

Oseltamivir is an oral agent that is generally well tolerated. Oseltamivir is available as an oral solution, which makes it the treatment of choice for influenza in infants and young children. Oseltamivir is not labeled for use in infants younger than 1 year, but dosing information for infants is available. During the 2009 H1N1 pandemic, the FDA provided dosing recommendations for infants as part of an Emergency Use Authorization. Although the authorization has now expired, the dosing information provided through the authorization is useful for practitioners who decide the risk of influenza-associated morbidity or mortality for a particular infant is higher than the potential risks of antiviral therapy for that infant. This information has been archived on the CDC's Web site (www.cdc.gov/h1n1flu/recommendations.htm). In 2011, the makers of oseltamivir changed the concentration of the oral solution from 12 mg/mL to 6 mg/mL because of excessive frothing with the higher concentration, which resulted in difficulty measuring accurate doses of the drug (Reference 68). Some wholesalers may still have the 12-mg/mL solution in supply, so pharmacists should carefully counsel parents or caregivers regarding the appropriate volume of medication to give their child. In recent years, nationwide shortages of the oral solution have also occurred. During times of shortage, an extemporaneous product with the final concentration of 15 mg/mL may be compounded from oseltamivir capsules using a recipe from the package insert. The most common adverse effects associated with oseltamivir use in children are nausea, vomiting, and diarrhea (Reference 69). Children and adolescents may also be at increased risk of neuropsychiatric disorders, such as hallucinations and abnormal behaviors that may result in harm, after oseltamivir administration (Reference 70). Table 3 describes appropriate oseltamivir dosing for children.

Zanamivir is available as a powder for inhalation and is packaged in its own unique delivery device called a Rotadisk (Reference 71). It is labeled for the treatment of influenza in children 7 years or older and for prophylaxis of influenza in children 5 years or older. Because of the device in which zanamivir is packaged, it cannot be nebulized into ventilators and is not effective for intubated children. Zanamivir's Rotadisk is also difficult for young children to use. It is not a pressurized canister and requires the recipient to inhale a forceful breath, which is difficult for young children to perform. Zanamivir is generally well tolerated. Phase III studies of children showed no significant difference in the adverse effects of zanamivir compared with placebo (Reference 71). Postmarketing surveillance of zanamivir use has shown a risk of bronchospasm after administration (Reference 71). As a result, zanamivir should not be used in children with preexisting pulmonary disease, such as asthma. Table 4 describes appropriate zanamivir dosing for children.

Table 3. Dosing of Oseltamivir for Children (Reference 61)

Age		Treatment	Postexposure Prophylaxis
< 14 days		3 mg/kg/dose daily	Not recommended unless critical situation
14 days to 2 months		3 mg/kg/dose twice daily	Not recommended unless critical situation
3–5 months		3 mg/kg/dose twice daily	3 mg/kg/dose daily
6–11 months		3 mg/kg/dose twice daily	3 mg/kg/dose daily
≥ 12 months	≤ 15 kg	30 mg twice daily	30 mg/day
	15.1–23 kg	45 mg twice daily	45 mg/day
	23.1–40 kg	60 mg twice daily	60 mg/day
	> 40 kg	75 mg twice daily	75 mg/day

Table 4. Dosing of Zanamivir for Children (Reference 61)

Age	Treatment	Postexposure Prophylaxis
Children < 5 years	Not recommended	Not recommended
Children 5–6 years	Not recommended	10 mg (2 inhalations) daily
Children ≥ 7 years	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) daily

Prophylaxis

Some children may benefit from antiviral prophylaxis with either oseltamivir or zanamivir when a community outbreak of influenza occurs. Children who should receive antiviral prophylaxis during community outbreaks (i.e., preexposure prophylaxis) include children at high risk of influenza complications with a contraindication to influenza vaccine, children at high risk of influenza complications if an outbreak occurs within 2 weeks of influenza vaccination, household contacts of unimmunized children at high risk of influenza complications, and household contacts of infants and children younger than 2 years (Reference 72). Once initiated, preexposure prophylaxis is most beneficial if administered for the duration of influenza activity in the community (Reference 61). When contemplating the initiation of postexposure prophylaxis, the practitioner should consider the exposed individual's risk of developing serious complications from influenza infection and the length of exposure to the infected individual. Postexposure prophylaxis should only be considered if antiviral therapy is initiated within 48 hours of exposure to the infected individual (Reference 61). Once postexposure prophylaxis is initiated, it is generally continued until 10 days after the last known exposure to an infected individual.

Conclusions

Otherwise-healthy children will receive only limited benefit, if any, from antiviral therapy. Antiviral therapy should be initiated in all children at high risk of complications from influenza infection, including those younger than 2 years and those with other comorbid conditions. Only the neuraminidase inhibitors (oseltamivir and zanamivir) should be used for the treatment or prophylaxis of influenza. Oseltamivir is the preferred antiviral agent in young children because it is available in an oral solution, and dosing information is available.

Community-Acquired Pneumonia

Epidemiology

According to the World Health Organization (WHO), pneumonia is the most common illness worldwide to cause death in children younger than 5 years (Reference 73). The WHO estimates that 1.8 million children died of pneumonia worldwide in 2009 (Reference 73). Mortality is highest in impoverished children who lack adequate resources to provide good nutrition or health care. Pulmonary complications that may result from pneumonia include pleural effusions, empyemas, lung abscesses, and necrotizing pneumonias. These complications often result in the need for admission to the intensive care unit and

mechanical ventilation. Children infected with typical bacterial organisms, such as *Streptococcus pneumoniae*, and those with mixed bacterial and viral infections are more likely to develop pleural effusions (Reference 74). Bacteremia can also result from pneumonia and lead to metastatic complications, such as meningitis, pericarditis, and septic arthritis (Reference 75). Adults who had childhood pneumonia before 7 years of age have been noted to have reduced pulmonary function (Reference 76). Factors that increase the risk of developing pneumonia in children include age younger than 5 years, recurrent upper respiratory tract infections, otitis media before 2 years of age, and a history of wheezing (Reference 77).

Etiology

The most common organism responsible for causing community-acquired pneumonia (CAP) in children varies by the child's age. Table 5 describes the most common organisms that cause pneumonia in children.

Viral Pneumonia

Viruses that commonly cause pneumonia in children include influenza A and B, RSV, human metapneumovirus, parainfluenza, adenovirus, human bocavirus, coronaviruses, and rhinoviruses (References 80–82). Viral and bacterial coinfection is common in children with pneumonia (Reference 74).

Table 5. Empiric Treatment of Community-Acquired Pneumonia in Children (References 75, 78, 79)

Age	Causative Organisms	First-line Therapy	Second-line Therapy
Birth to 3 weeks	*Escherichia coli*	Ampicillin + gentamicin	Ampicillin + cefotaxime
	Group B *Streptococcus*		
	Listeria monocytogenes		
	Haemophilus influenzae	Third-generation cephalosporin	
3 weeks to 3 months	Viruses	Supportive care	
	Chlamydia trachomatis	Azithromycin	
	Streptococcus pneumoniae	High-dose amoxicillin	Azithromycin, oral third-generation cephalosporin, clindamycin
		Third-generation cephalosporin in hospitalized infants	Vancomycin
	H. influenzae	Third-generation cephalosporin	
4 months to 4 years	Viruses	Supportive care	
	Chlamydia pneumoniae *Mycoplasma pneumoniae*	Azithromycin	Doxycycline,[a] fluoroquinolone[b]
	S. pneumoniae	High-dose amoxicillin	Azithromycin, oral third-generation cephalosporin, clindamycin, levofloxacin[b]
		Third-generation cephalosporin in hospitalized infants	Vancomycin, levofloxacin[b]
≥ 5 years	*C. pneumoniae* *M. pneumoniae*	Azithromycin	Doxycycline,[a] fluoroquinolone[b]
	S. pneumoniae	High-dose amoxicillin	Azithromycin, oral third-generation cephalosporin, clindamycin, levofloxacin[b]
		Third-generation cephalosporin in hospitalized infants	Vancomycin, levofloxacin[b]
Empyema, lung abscess, necrotizing pneumonia	*S. pneumoniae*	Vancomycin Clindamycin	Ceftriaxone,[c] doxycycline,[a] levofloxacin[b]
	S. aureus (including MRSA)	Vancomycin Clindamycin	Doxycycline,[a] linezolid

[a]Doxycycline should not be used in children < 8 years because of discoloration of permanent teeth.
[b]The use of fluoroquinolones in children should be avoided unless no other safe alternatives are available.
[c]Ceftriaxone should only be used if cultures show the absence of MRSA.
MRSA = methicillin-resistant *Staphylococcus aureus*.

Bacterial Pneumonia

During the neonatal period, group B *Streptococcus* and gram-negative enteric organisms, especially *Escherichia coli,* are the most common causes of pneumonia (Reference 75). *S. pneumoniae* is the most likely bacterial cause of pneumonia in infants and children (Reference 75). *M. pneumoniae* and *C. pneumoniae* are common causes of bacterial pneumonia in children older than 5 years (Reference 78). Other, less common bacteria associated with pneumonia in children include *Staphylococcus aureus*, *B. pertussis*, group A *Streptococcus*, *Moraxella catarrhalis*, *Haemophilus influenzae*, and *Mycobacterium tuberculosis* (References 75, 78). Tuberculosis will not be discussed in this chapter. Refer to the CDC guidelines at www.cdc.gov for information regarding the proper assessment and medical management of a child with tuberculosis.

Clinical Presentation

The most common symptoms associated with pneumonia in children are fever and cough, with fever present in more than 90% of children with pneumonia (References 75, 78, 80). Bacterial pneumonia usually has a rapid onset and may include productive cough and chest pain (Reference 75). Other signs or symptoms of pneumonia that may be present include tachypnea, difficulty breathing, retractions, grunting, wheezing, and crackles (References 75, 80). In children, tachypnea is defined as greater than 50 breaths/minute in infants 2–12 months of age, greater than 40 breaths/minute in children 1–5 years of age, and greater than 20 breaths/minute in children 6 years and older (Reference 78). Some children with pneumonia may have nonspecific symptoms of nausea, vomiting, and abdominal pain (Reference 75). Children who develop pneumonia from atypical organisms may present with symptoms of fever, cough, sore throat, and malaise that develop slowly, usually over 3–5 days (Reference 83).

Diagnosis

The presence of infiltrates on chest radiograph is considered the gold standard for diagnosing pneumonia (Reference 80). For an afebrile child with a clinical presentation strongly suggestive of pneumonia, radiography is not necessary for determining proper outpatient management. Chest radiography is recommended for infants and children with hypoxia or respiratory distress, for infants or children who do not respond to an initial course of antibiotics, and for all infants or children admitted to the hospital with pneumonia (Reference 83). Bacterial pneumonias often exhibit lobar infiltrates, whereas atypical pneumonias often exhibit perihilar infiltrates, although these findings are nonspecific and can also be seen in viral pneumonias (Reference 75). Pneumonias caused by atypical organisms may exhibit patchy infiltrates bilaterally (Reference 78). Children with pneumonia often have elevated white blood cell counts and C-reactive protein; however, these laboratory parameters are nonspecific and not helpful in differentiating bacterial from viral pneumonia (References 75, 78, 80).

Blood cultures are positive less than 10% of the time when pneumococcal pneumonia is present (Reference 78). As a result, they should not be obtained routinely in children who are treated for CAP as outpatients. Blood cultures should be performed if a child fails to improve on antimicrobial therapy, shows clinical deterioration, or has disease progression (Reference 83).

Sputum cultures are not routinely performed in children. Obtaining a culture of the throat or respiratory secretions may not accurately reflect the organisms that are causing infection in the lower respiratory tract and may result in the inappropriate use of antimicrobials (Reference 84). Unfortunately, for most bacteria, the only way to confirm the causative organism is to obtain a bacterial culture from pleural fluid or an empyema, if present. Polymerase chain reaction tests that measure the presence of DNA are available for some organisms, such as *M. pneumoniae*, and should be used when a child presents with symptoms consistent with pneumonia from atypical organisms (References 83, 84). Viral antigen testing is not helpful in differentiating bacterial from viral pneumonia because the presence of a virus does not exclude a bacterial process, although it may be useful for infection control in a hospital setting.

Prevention

Vaccination against influenza, *S. pneumoniae*, and *H. influenzae* type B can markedly decrease a child's risk of developing pneumonia. Since the introduction of the pneumococcal conjugate vaccine in 2000, the incidence of hospitalization because of pneumonia from any cause has decreased by 33% in children, and the incidence of hospitalization from pneumococcal pneumonia has decreased by 61% (Reference 85). Refer to the Pediatric Vaccines chapter for a more detailed discussion of these vaccines.

Treatment

The primary goals of therapy for CAP are to eradicate the infection and prevent the development of complications, such as empyema, necrotizing pneumonia, or death. Children who are afebrile and not critically ill (e.g., without hypoxia or signs of respiratory distress) may be treated as outpatients. Infants and children with suspected pneumonia in the following situations should be hospitalized: those younger than 6 months; those who appear dehydrated or cannot tolerate oral liquids;

those with respiratory distress or persistent hypoxia; those with CAP caused by a highly virulent organism (e.g., community-associated methicillin-resistant *S. aureus* [CA-MRSA]); and those who may have unreliable family or social situations that make follow-up difficult (References 75, 78, 83). Hospital admission should also be considered for children with underlying chronic medical conditions or children whose outpatient management has failed. Because recovery of the causative organism is rare in children with CAP, treatment is usually empiric and should include coverage of the organisms most likely to cause pneumonia in the child's age group.

Viral Pneumonia

Children who are younger than 5 years typically develop pneumonia from viral pathogens. A child with viral pneumonia should be treated with supportive care because antibiotics are not effective in this situation. Antipyretics such as acetaminophen or ibuprofen may be useful for children with a low-grade fever. Children with viral pneumonia should be encouraged to maintain good fluid intake to avoid dehydration. Antivirals should be used in infants or children infected with influenza who are at high risk of complications from infection.

Neonatal Pneumonia

During the neonatal period (up to 1 month of age), pneumonia is typically caused by pathogens that colonize the genitourinary tracts of pregnant women, specifically group B *Streptococcus* and *E. coli*. Neonates with bacterial pneumonia should be hospitalized to manage potential respiratory distress and facilitate the use of intravenous antibiotics. Empiric therapy should consist of ampicillin and an aminoglycoside (usually gentamicin) or a third-generation cephalosporin (usually cefotaxime). Ceftriaxone should not be used in this population because of the risk of kernicterus.

Pneumococcal Pneumonia

The treatment of choice for pneumococcal CAP in children receiving outpatient therapy is amoxicillin (References 78, 83, 84). Amoxicillin should be administered at a dose of 80–100 mg/kg/day divided two or three times/day to adequately treat penicillin-resistant *S. pneumoniae* (PRSP) (References 78, 84). *S. pneumoniae* exhibits resistance to β-lactam antibiotics by alterations to penicillin-binding proteins, which often can be overcome by high doses of β-lactams (Reference 86). Because pneumococci do not produce β-lactamases, amoxicillin/clavulanate has no additional benefit in the treatment of pneumococcal pneumonia (Reference 84). For children with an allergy or intolerance to amoxicillin, a second- or third-generation cephalosporin may be used unless the child has had a type 1 hypersensitivity reaction to β-lactam antibiotics (Reference 83). Other alternatives for outpatient management of CAP include levofloxacin (if susceptible) or linezolid. Clindamycin is another viable alternative if community resistance rates are low (typically, less than 10%). Once treatment is initiated, symptomatic improvement should occur within 48–72 hours. If a child does not respond to therapy, further evaluation is warranted to rule out other causes of the child's symptoms. Therapy duration for outpatient management of CAP in children is typically 7–10 days.

For children who require hospitalization, intravenous antibiotics should be used. If *S. pneumoniae* has been isolated in a child with CAP, therapy should be selected on the basis of the penicillin minimum inhibitory concentration (MIC) for the organism. For *S. pneumoniae* isolates with a penicillin MIC of 2 mcg/mL or less, ampicillin or aqueous penicillin G is preferred (Reference 83). Aternative for *S. pneumoniae* with a penicillin MIC of 2 mcg/mL or less are ceftriaxone, cefotaxime, clindamycin (if susceptible), or vancomycin. For *S. pneumoniae* isolates with a penicillin MIC of 4 mcg/mL or higher, ceftriaxone is the preferred agent. Alternative agents for isolates of *S. pneumoniae* with a penicillin MIC of 4 mcg/mL or higher include high-dose ampicillin, clindamycin (if susceptible), vancomycin, levofloxacin, or linezolid. For children hospitalized with CAP, the therapy duration is typically 10–14 days. Longer treatment durations may be necessary in children who develop complications, such as lung abscesses or necrotizing pneumonia.

Pneumonia Caused by Atypical Organisms

Empiric coverage of atypical organisms should be added to pneumococcal coverage in both the inpatient and outpatient management of CAP beyond the neonatal period whenever there is a high degree of suspicion that an atypical organism is present. Macrolide antibiotics are generally the preferred treatment for the atypical organisms (*M. pneumoniae*, *C. pneumoniae*, and *Chlamydia trachomatis*). Azithromycin is the preferred macrolide antibiotic in children because of its tolerability and shorter treatment duration. Azithromycin should be administered at a dose of 10 mg/kg on day 1 and then 5 mg/kg/day on days 2–5 (References 78, 84). For children who may be at risk of not adhering to therapy, azithromycin may alternatively be administered at 10 mg/kg/day for 3 days. For children unable to tolerate oral medications, azithromycin is also available in an injectable form. Because of increasing resistance rates of *S. pneumoniae* to macrolides, empiric therapy

for pneumonia beyond the neonatal period should include a β-lactam antibiotic in addition to azithromycin. For children in whom coverage of atypical organisms is warranted but who have an allergy or intolerance to macrolide antibiotics, doxycycline or a fluoroquinolone may be used (Reference 87). Doxycycline should not be used in children younger than 8 years because of the risk of permanent tooth staining. Fluoroquinolones have shown joint toxicities in studies of juvenile animals. Although permanent joint damage has not been observed in children, the AAP recommends that the use of fluoroquinolones be reserved for situations when safe alternative therapies are not available (Reference 88).

Conclusions

Children who have viral pneumonia should be treated with supportive care. Antibiotics offer no benefit to children with viral pneumonia. Pneumococcus is a common cause of bacterial pneumonia in children and can be treated using high-dose amoxicillin in an ambulatory setting, even for penicillin-resistant *S. pneumoniae*. Empiric therapy for pediatric CAP should include amoxicillin and azithromycin when there is a high degree of suspicion that an atypical organism is contributing to disease.

Lung Abscesses, Empyemas, and Necrotizing Pneumonias

Epidemiology

Lung abscesses, empyemas, and necrotizing pneumonias are some of the more serious complications associated with CAP in children. The incidence of these complications of CAP in children has increased during the past 10–15 years (References 85, 89–91). An increase in the incidence of complications of CAP from pneumococcal serotypes not contained in the heptavalent vaccine has also been reported (References 85, 92). One study reported that children who had been treated with antibiotics or ibuprofen for CAP before hospitalization had an increased risk of developing an empyema. In addition to having more severe disease, children with empyemas were more likely to have a fever lasting more than 7 days and the presence of chest pain, which suggests a more prolonged disease course (Reference 89). Additional risk factors for empyemas include children 3 years and older and children with varicella infection within 1 month of hospitalization (Reference 89).

Etiology

Organisms most commonly associated with empyemas and necrotizing pneumonias are *S. pneumoniae*, *S. aureus* (including methicillin-resistant *S. aureus* [MRSA]), and group A *Streptococcus* (References 78, 85, 89–94). Other organisms that have been isolated in children with empyemas or necrotizing pneumonia include *M. pneumoniae*, *Streptococcus milleri*, viridans streptococci, *H. influenzae*, *Fusobacterium* spp., *Eikenella* spp., *Pseudomonas aeruginosa*, other gram-negative organisms, and *M. tuberculosis* (References 78, 90, 94–98).

Clinical Presentation

Symptoms of empyema or necrotizing pneumonia may be similar to those seen with CAP and include fever, tachypnea, and chest pain (References 78, 94). The development of symptoms in someone with an empyema or necrotizing pneumonia is generally a more insidious process than what is typically seen with CAP. A child with an empyema or necrotizing pneumonia will generally be more ill-appearing than will a typical child with CAP and may present with chest pain and splinting (Reference 78). On physical examination, absent or diminished breath sounds may be noted, as well as dullness upon percussion of the chest wall (References 78, 94). Empyemas rarely cause increased mortality in children (Reference 97).

Diagnosis

Chest radiographs are often performed to document the presence of pneumonia, but they are not sensitive enough to confirm the presence of an empyema (Reference 97). Necrotizing pneumonias and cavitations may be detected by chest radiograph. Any child who presents with a cavitary lesion on chest radiography should be evaluated for tuberculosis. Ultrasonography may be useful for differentiating a pleural effusion from a loculated fluid collection, which may require surgical intervention (Reference 97). A chest computed tomography (CT) may also be helpful for diagnosing an empyema; however, it should not be used routinely for children with pneumonia because of the high-radiation exposure dose associated with CTs (Reference 97). Sputum and throat cultures are not helpful in identifying the organism responsible for causing empyema or necrotizing pneumonia in children. If surgical drainage of a fluid collection, empyema, or abscess is performed, the material should be sent to the microbiology laboratory for Gram stain and culture to provide targeted antimicrobial therapy.

Treatment

The goals of therapy for the treatment of empyemas, lung abscesses, or necrotizing pneumonia are to limit the destruction of lung tissue and prevent further morbidity or mortality.

Surgical Management

Many children with empyemas will require surgical intervention to improve lung function and speed the healing process. Whether to perform surgical drainage of an empyema early in the course of disease is controversial. In one study, about one-half of the children evaluated were

successfully treated with antibiotics alone (Reference 99). Children who were treated with only antibiotics had significantly shorter lengths of hospital stay, fewer days of fever during hospitalization, and fewer days of intravenous antibiotics (Reference 99). Children who required surgical drainage were more likely to be younger, have a large effusion, have a loculated effusion, have a mediastinal shift, or require mechanical ventilation (Reference 99). These data suggest children with small effusions who are not in danger of respiratory compromise can be managed with antibiotic therapy alone.

Pharmacologic Therapy

Empiric therapy for children with empyemas or necrotizing pneumonias should include coverage of *S. pneumoniae* and *S. aureus,* including MRSA (Reference 101). If thoracentesis or a video-assisted thoracoscopic surgical procedure is performed and bacterial cultures are obtained, then definitive antibiotic therapy should be targeted at the specific organisms identified once final identification and sensitivity results are known. The typical duration of therapy for an empyema or necrotizing pneumonia is 2–4 weeks.

Antibiotics for the Management of Complications from CAP

Third-Generation Cephalosporins

Ceftriaxone is most commonly used as monotherapy for the treatment of empyemas and necrotizing pneumonias caused by *S. pneumoniae*, even when the penicillin MIC is 4 mcg/mL or greater (Reference 83) (Table 6). Cefotaxime is an acceptable alternative to ceftriaxone at institutions where ceftriaxone is not on formulary. Ceftriaxone has only moderate activity, at best, against *S. aureus*, and no activity against MRSA (References 78, 87). As a result, it should not be used as monotherapy for empiric therapy in a child with an empyema or necrotizing pneumonia. Ceftriaxone also shows good activity against many gram-negative organisms, except for *P. aeruginosa*, *Enterobacter* spp., and *Citrobacter* spp. Ceftriaxone should be administered at a dose of 100 mg/kg/day intravenously given once or twice daily and is generally well tolerated. Adverse effects may include cholelithiasis and gallbladder sludging. The second- and third-generation cephalosporins (e.g., cefpodoxime, cefuroxime, cefprozil) are acceptable agents for step-down oral therapy when a child with an empyema is stable enough to transition to outpatient therapy.

Vancomycin

Vancomycin is typically used empirically in combination with a third-generation cephalosporin for the treatment of empyemas and necrotizing pneumonias. Vancomycin has good coverage against *S. pneumoniae*, *S. aureus*, and MRSA (References 81, 86). Vancomycin has lower tissue penetration and slower antibacterial activity than other antibiotics typically used for pneumonia. As a result, vancomycin should be discontinued if an organism other than MRSA is identified and the child can tolerate the antibiotic of choice, or a reasonable alternative, for the identified organism. Vancomycin should be initiated at a dose of 15 mg/kg intravenously every 6 hours in most children (Reference 101). Some clinicians may prefer to initiate vancomycin at 8-hour intervals, especially in adolescents. Vancomycin peaks should not be monitored routinely. Vancomycin troughs should target a goal of 15–20 mcg/mL (Reference 102). The most common adverse effect associated with vancomycin is red man syndrome, which may include flushing of the face and neck from histamine release. Extending the vancomycin infusion time generally prevents further episodes of red man syndrome. Nephrotoxicity has also been associated with vancomycin administration, although this effect is more common with the concurrent administration of other nephrotoxic agents or in children who become dehydrated (Reference 102).

Clindamycin

Clindamycin is a reasonable alternative to vancomycin for the treatment of empyemas and necrotizing pneumonias caused by *S. pneumoniae* or *S. aureus* (if susceptible). It can be used in combination with a third-generation cephalosporin for empiric therapy or as monotherapy, if the causative organism is susceptible. Clindamycin has excellent oral bioavailability, so it has the advantage of offering an oral dosage form in children who are stable and can tolerate oral therapy. Clindamycin has good activity against staphylococci and streptococci, but CA-MRSA resistance is increasing. The Infectious Diseases Society of America recommends clindamycin not be used empirically when community resistance rates for MRSA are greater than 10% (Reference 101). If *Staphylococcus* is identified from a child with an empyema or necrotizing pneumonia, the practitioner should note the erythromycin susceptibility results in addition to the clindamycin susceptibility results. Methicillin-resistant *S. aureus* has the potential to carry a gene (*erm*) that codes for inducible clindamycin resistance (Reference 103). If a MRSA strain shows erythromycin resistance but is susceptible to clindamycin during the initial susceptibility testing, a disk diffusion test (also called a D-test) should be performed to rule out the presence of inducible clindamycin resistance (References 101, 103). Clindamycin is an acceptable choice for step-down oral therapy in children ready to transition to oral therapy, if the organism is susceptible. Clindamycin is typically administered at a dose of 40 mg/kg/day intravenously

Table 6. Dosing of Antibiotics Used for Pediatric Respiratory Tract Infections (References 83, 100)

Antibiotic	Neonates[a]	Infants and Children
Amoxicillin	30 mg/kg/day divided BID	80–100 mg/kg/day divided TID
Amoxicillin/ Clavulanate	30 mg/kg/day divided BID	80–100 mg/kg/day divided TID
Ampicillin	50–100 mg/kg/day divided BID or QID	150–200 mg/kg/day divided QID 300–400 mg/kg/day divided QID for PRSP
Azithromycin	10 mg/kg/day	10 mg/kg on day 1; then 5 mg/kg day on days 2–5; OR 10 mg/kg/day for 3 days
Aztreonam	60–90 mg/kg/day divided BID or TID	90–120 mg/kg/day divided TID or QID
Cefazolin	40–60 mg/kg/day divided BID or TID	50–100 mg/kg/day divided TID
Cefepime	30 mg/kg/dose BID	50 mg/kg/dose BID
Cefotaxime	100 mg/kg/day divided BID	100–200 mg/kg/day divided TID
Ceftazidime	100 mg/kg/day divided BID	100–150 mg/kg/day divided TID
Ceftriaxone	Avoid	50–100 mg/kg/day QD or divided BID
Ciprofloxacin	Avoid	20–30 mg/kg/day divided BID
Clindamycin	15–30 mg/kg/day divided TID or QID	30 mg/kg/day divided TID or QID
Doxycycline	Avoid	2–4 mg/kg/day QD or BID
Gentamicin	3.5–5 mg/kg/day QD	2.5 mg/kg/dose TID or 5–7.5 mg/kg/day QD
Levofloxacin	Avoid	10 mg/kg/dose BID for children younger than 5 years; 10 mg/kg/dose QD for children 5 years and older
Linezolid	10 mg/kg/dose BID or TID	10 mg/kg/dose TID for children younger than 12 years, 10 mg/kg/dose BID for children 12 years and older
Meropenem	20 mg/kg/dose BID or TID	20 mg/kg/dose TID
Nafcillin	75–140 mg/kg/day divided TID or QID	100–200 mg/kg/day divided QID
Oxacillin	100–200 mg/kg/day divided TID or QID	150–200 mg/kg/day divided QID
Piperacillin/ Tazobactam	150–300 mg/kg/day divided TID or QID	200–300 mg/kg/day divided TID or QID
Ticarcillin/ Clavulanate	225–300 mg/kg/day divided TID	200–300 mg/kg/day divided QID
TMP/SMX[b]	Avoid	10–12 mg/kg/day divided BID
Tobramycin	3.5–5 mg/kg/day QD	2.5 mg/kg/dose TID or 5–7.5 mg/kg/day QD

[a]Dosing for full-term neonates.

[b]Dosed on the basis of the TMP component.

BID = twice daily (or every 12 hours); PRSP = penicillin-resistant *Streptococcus pneumoniae*; QD = daily; QID = four times/day (or every 6 hours); TID = three times/day (or every 8 hours); TMP/SMX = trimethoprim/sulfamethoxazole.

divided every 6–8 hours. The most common adverse effects associated with clindamycin are diarrhea (including *Clostridium difficile*–associated diarrhea) and taste intolerance for children who receive the oral liquid.

Doxycycline

Doxycycline generally has good coverage against *S. aureus*, including MRSA, but it is not a good empiric choice for empyemas or necrotizing pneumonia in most children because of the risk of tooth discoloration and possible resistance. If a MRSA isolate sensitive to doxycycline is recovered in a child with an empyema, doxycycline is a reasonable alternative to vancomycin for step-down oral monotherapy. It is also a reasonable alternative to macrolides if coverage of atypical organisms is desired in a child who is allergic or intolerant. Doxycycline also has excellent oral bioavailability, and when the child can tolerate oral antibiotics, it can easily be transitioned to oral therapy. Doxycycline should be administered orally or intravenously at a dose of 2 mg/kg every 12 hours.

Linezolid

Linezolid has good activity against most staphylococcal and streptococcal species, including MRSA, PRSP, and vancomycin-resistant enterococci. It has excellent oral bioavailability and offers an acceptable alternative to oral monotherapy on an outpatient basis. Although resistance to linezolid is rare, its use is limited by its high cost and high rate of thrombocytopenia, especially when used for more than 2 weeks (Reference 101). The average wholesale price of linezolid is around $460 for a 150-mL bottle of 100 mg/5 mL suspension and around $92 per tablet (600 mg) (Reference 22). For children younger than 12 years, linezolid is typically administered at a dose of 10 mg/kg every 8 hours. For children 12 years and older, it is typically administered at a dose of 10 mg/kg every 12 hours.

Fluoroquinolones

Fluoroquinolones have broad-spectrum activity against many gram-positive and gram-negative organisms, with the exception of ciprofloxacin, which predominantly has gram-negative activity. Levofloxacin is the fluoroquinolone with gram-positive activity that is most often used in children because of its well-established dosing information. Levofloxacin generally has good activity against *S. pneumoniae* and may exhibit in vitro activity against MRSA; however, it should not be used routinely for MRSA because resistance develops when used as monotherapy (Reference 101). Ciprofloxacin is a reasonable choice for the treatment of an empyema or necrotizing pneumonia caused by gram-negative organisms such as *P. aeruginosa*; however, it lacks activity against *S. pneumoniae*. The fluoroquinolones also have very good oral bioavailability and may be used as step-down therapy for children who are transitioning to outpatient therapy. For children 5 years and older, levofloxacin is typically administered at 10 mg/kg once a day. Ciprofloxacin may be administered at a dose of 10–15 mg/kg/dose every 12 hours, regardless of the child's age.

Conclusions

Empiric therapy for empyemas, lung abscesses, and necrotizing pneumonias should include coverage of the organisms most commonly associated with these processes—*S. pneumoniae*, group A *Streptococcus*, and *S. aureus* (including MRSA). Many treatment options exist for these complications of CAP. Vancomycin in combination with a third-generation cephalosporin is often the mainstay of therapy until a definitive organism and its susceptibilities are identified. Therapy duration for these complications of CAP is not well defined and should be individualized on the basis of the child's response. Treating a child with 3–4 weeks of antibiotics for an empyema, lung abscess, or necrotizing pneumonia is common.

Chapter Conclusions

Lower respiratory tract infections are a significant cause of hospitalizations in children and are among the most common reasons for a child to be seen in a primary care physician's office. Many LRTIs that are caused by viral infections respond well to symptom management. Bacterial LRTIs often require antibiotic therapy to prevent the transmission of the disease to other susceptible individuals and to limit the development of complications.

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CHAPTER 38

Infectious Diarrhea

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Learning Objectives

1. Describe the epidemiology of and risk factors for infectious diarrhea in children.
2. Identify when oral rehydration solutions are appropriate for treating dehydration in children with infectious diarrhea.
3. Describe the clinical presentation of each gastrointestinal infection in children.
4. Recommend appropriate therapies for children with infectious diarrhea.
5. Discuss preventive measures that can protect children from gastrointestinal infections.

Abbreviations in This Chapter

CDI	*Clostridium difficile* infection
EAEC	Enteroaggregative *Escherichia coli*
EHEC	Enterohemorrhagic *Escherichia coli*
EIEC	Enteroinvasive *Escherichia coli*
EPEC	Enteropathogenic *Escherichia coli*
ETEC	Enterotoxigenic *Escherichia coli*
HUS	Hemolytic-uremic syndrome
ORS	Oral rehydration solution
ORT	Oral rehydration therapy

Introduction

Infectious diarrhea accompanied by dehydration is the second leading cause of global pediatric morbidity and mortality, resulting in more than 1.5 million deaths annually in children younger than 5 years (Reference 1). More than 80% of pediatric deaths from infectious diarrhea occur in Africa and South Asia (Reference 1). In the United States, acute gastrointestinal infections are less common than in the developing world, and the elderly are at the highest risk of death. However, infectious diarrhea and dehydration still account for about 200,000 hospitalizations and 300 deaths annually among children in the United States (Reference 2).

Diarrhea, defined as having unusually loose or watery stools at least three times/day or more than usual for an individual, is frequently a symptom of gastrointestinal infections. Viruses are the most common cause of pediatric infectious diarrhea worldwide, but bacteria and parasites also play a role. Significant diarrhea can lead to dehydration, which commonly occurs with cholera or after infection with rotavirus or enterotoxigenic *Escherichia coli* (ETEC). Management of infectious diarrhea focuses on preventing and treating dehydration and its complications in addition to limiting the spread of infection to others, which occurs mainly by the oral-fecal route.

Several factors increase the risk of spreading gastrointestinal infections and developing diarrhea and its complications. The most significant risk factor for contracting infection is behavior that increases the likelihood of fecal contact, including lack of handwashing after defecation or handling feces before handling food. In addition, day care attendance and living in crowded conditions increase the risk of contact with contaminated excrement. Ingestion of certain foods and exposure to reptiles or other pets increase the risk of exposure to specific infecting pathogens. In developing countries, polluted water sources, poor sanitation practices, contaminated food, and malnutrition contribute to the spread and severity of infectious diarrhea (Reference 1). International travel to developing countries can result in traveler's diarrhea after the consumption of contaminated food or water.

Children and immunocompromised individuals have an increased risk of dehydration and severe disease from gastrointestinal infections. Water makes up a greater proportion of body weight in children than in adults, and children use more water to support metabolism and conserve less water through their kidneys. Thus, acute body water losses that occur with diarrhea have a greater effect in children, increasing the risk of dehydration. Immunocompromised conditions and the relatively immature immune system in young children contribute to more severe illness from gastrointestinal infections.

Rehydration Therapy

Fluid replacement, electrolyte balance, and maintenance of normal feeding are vital components for managing dehydration from infectious diarrhea, regardless of the cause. The appropriate route of administration for replacement fluids depends on the severity of dehydration, as characterized by percent loss in body weight and clinical presentation. Table 1 displays the clinical signs and symptoms that are useful for categorizing dehydration in children and the recommended

Table 1. Clinical Signs and Symptoms and Fluid Replacement Therapies Associated with Degree of Dehydration in Children

Sign or Symptom or Therapy	Minimal or No Dehydration (< 3% Loss of Body Weight)	Mild to Moderate Dehydration (3% to 9% Loss of Body Weight)	Severe Dehydration (> 9% Loss of Body Weight)
Mental status	Normal; alert	Normal to fatigued or irritable	Lethargic, apathetic; unconscious
Fontanelle	Normal	Normal to sunken	Sunken
Eyes	Normal	Sunken orbits; decreased tears	Deeply sunken orbits; absent tears
Mucous membranes	Normal; moist	Slightly dry to dry	Parched
Thirst	Normal	Thirsty	Too lethargic to drink
Heart rate	Normal	Normal to increased	Increased; bradycardia in severe cases
Quality of pulse	Normal	Normal to decreased	Weak or not palpable
Blood pressure	Normal	Normal	Normal to reduced
Respirations	Normal	Normal to fast	Deep
Skin turgor	Normal recoil	Decreased recoil < 2 seconds	Recoil > 2 seconds
Extremities	Warm; normal capillary refill	Cool; delayed capillary refill	Cold, mottled, cyanotic; prolonged capillary refill
Urine output	Normal to decreased	Decreased	Minimal
Fluid replacement therapy	None	Oral rehydration therapy (ORT) at 50–100 mL/kg over 2–4 hours	Intravenous (IV) bolus of lactated Ringer's solution or normal saline 20 mL/kg (over 15–30 minutes) until perfusion and mental status improve; then IV fluids (5% dextrose with ½ normal saline) at twice maintenance rate or ORT 100 mL/kg over 4 hours

Adapted from References 2 and 3.

replacement fluids for each stage. Severe dehydration should be treated initially with intravenous fluids, whereas mild to moderate dehydration is best managed with oral rehydration therapy (ORT) (References 2–6).

Severe Dehydration

Severe dehydration is a medical emergency that requires immediate and rapid rehydration to avoid vital organ damage from low tissue perfusion. Intravenous resuscitation should occur with lactated Ringer's solution or normal saline using an initial bolus dose of 20 mL/kg for most children. Children who are frail or malnourished should receive 10 mL/kg to avoid edema from reduced cardiac output (Reference 2). Several bolus doses may be necessary and should be given until pulse, perfusion, and mental status are normalized. Once these parameters have stabilized, rehydration therapy can be switched to the oral route when tolerated.

Mild to Moderate Dehydration

Oral rehydration is highly effective for treating mild to moderate dehydration and has the advantages of being noninvasive, inexpensive, and capable of being administered at home (References 2, 3). Development of glucose-based oral rehydration solutions (ORS) was based on the principle of coupled glucose and sodium transport. These nutrients are co-absorbed across intestinal brush border luminal cell membranes into enterocytes, where they are then pumped into the bloodstream through different transmembrane transporter systems. Water reabsorption occurs because of the osmotic gradient generated by these transport systems, which remain intact even in severe diarrhea (Reference 2). Mixtures of ORS, which contain water, salts, and glucose, are recommended to have low osmolarity (about 245 mmol/L) to reduce the stool output and vomiting associated with solutions with high osmolarity (Reference 6). Additional information on the management of dehydration from diarrhea can be found in the Diarrhea and Constipation chapter.

Nonbacterial Causes of Infectious Diarrhea

Viral Gastroenteritis

Viruses cause more than one-half of all pediatric diarrheal illnesses, which can occur in epidemics or as sporadic illnesses. Viruses that cause gastroenteritis include rotavirus, noroviruses, enteric adenoviruses, astroviruses,

and coronaviruses. Rotavirus is a predominant cause of infectious diarrhea worldwide, infecting all children by age 5 years (Reference 7; more information can be found in the Pediatric Vaccines chapter). Immunity is usually incomplete after an initial rotavirus infection, but it may be protective against more severe illness after subsequent infection. Noroviruses are responsible for around 50% of all gastroenteritis outbreaks, and they were recently reported as the leading cause of acute infectious diarrhea in the United States in all age groups (Reference 8). Noroviruses are highly contagious and are spread through contaminated food and water, creating outbreaks in institutions such as health care facilities, schools, and child care centers, as well as on cruise ships. Immunity to norovirus infection is complex and may depend more on innate host factors (such as cell receptor mutations that block viral entry into host cells) than on antibody development.

Ingestion of viruses through contaminated food or water or after contact with contaminated surfaces can lead to significant diarrhea and dehydration. Viruses directly damage the intestinal lining, leading to impaired absorption and subsequent fluid and electrolyte loss. Brush border enzyme activity is reduced, which can result in transient lactose intolerance. After an incubation of 12 hours to 3 days, clinical manifestations of viral gastroenteritis develop, which often begin with vomiting. Nonbloody diarrhea, abdominal cramping, and nausea are usually present. Viral gastrointestinal infection can also be asymptomatic or associated with extraintestinal symptoms such as fever, myalgia, headache, or malaise. Symptoms typically resolve in 12–48 hours for norovirus infection or 3–7 days for rotavirus. Diagnosis of viral gastroenteritis is made by detecting stool viral antigens through enzyme immunoassay, latex agglutination assay, or polymerase chain reaction (PCR).

Treatment of viral diarrhea is mainly supportive. Rehydration with ORS or intravenous solutions replaces fluids and electrolytes lost through stool or vomitus. Children should continue their normal diet when possible, but foods and liquids high in simple sugars should be avoided because they can aggravate diarrhea. Probiotics containing *Lactobacillus rhamnosus* GG in doses of 10 billion colony-forming units have been shown to reduce the amount and duration of diarrhea by about 1 day when given to children early in the course of rotavirus infection (References 9–11). Probiotics should not be used in children with short gut syndrome or immunodeficiencies because of the risk of bacteremia and sepsis from probiotic strains. Loperamide, an opioid antimotility agent, may reduce the duration of viral diarrhea, but it is not recommended for children younger than 3 years or in those who are malnourished, who are moderately to severely dehydrated, or who have bloody diarrhea (Reference 12). These patient groups are at high risk of adverse events such as lethargy, ileus, and respiratory depression. Antimicrobials have no role in the management of viral gastroenteritis.

Zinc supplementation may reduce the duration of acute viral diarrhea in children who are at least 6 months of age and at risk of zinc deficiency (References 2, 13). Developing countries have high rates of malnutrition and zinc deficiency; zinc is poorly absorbed from grains, nuts, and legumes, whereas high levels of zinc are found in meat and fish. Zinc promotes a healthy gastrointestinal tract mucosa and restores brush border enzyme activity in addition to stimulating immunity against gastrointestinal pathogens (References 6, 13). Zinc doses of 10–20 mg/day given for 10–14 days should be considered for children with acute viral diarrhea, particularly those who are malnourished or at risk of zinc deficiency (References 6, 13).

Prevention of viral gastroenteritis focuses on proper hygiene and vaccination. Handwashing with plain soap and running water for at least 20 seconds is essential for caregivers and individuals with diarrheal illness, particularly after defecation or potential contact with feces and before food preparation and ingestion. Hand sanitizers are an alternative to handwashing but should not be considered a substitute (Reference 8). Handwashing may be more effective at removing viral organisms from the skin through its mechanical process than alcohol-based hand sanitizers. The only vaccine available to protect against diarrheal illness is the rotavirus vaccine recommended for infants (refer to the Pediatric Vaccines chapter for more information).

Parasitic Gastrointestinal Infections

Infectious diarrhea can be caused by parasites in both the developing world and industrialized nations. In the United States, *Giardia lamblia* and *Cryptosporidium* are two protozoan parasites that commonly infect immunocompromised and immunocompetent children. Giardiasis is reviewed in the Parasitic Infections in Pediatrics chapter; thus, this section will focus on cryptosporidiosis.

Cryptosporidiosis is widespread in the United States and has increased in all states in recent years. In 2008, 3.5 cases were reported per 100,000 population; the highest incidence was in children between 1 and 9 years of age, and the peak time for infection was during summer and early fall (Reference 14). *Cryptosporidium* is often transmitted through recreational water such as swimming pools or through exposure to infected animals, particularly cattle. Risk factors for cryptosporidiosis include the use of public swimming pools or other freshwater sources, contact with cattle or incontinent children, international travel to areas of high endemicity, immunodeficiency, and consumption of a large amount of unboiled well water.

Cryptosporidiosis occurs after the ingestion of *Cryptosporidium* oocysts found in fecally contaminated food or water or through direct person-to-person contact. Infection is usually limited to the intestinal surface epithelia where the parasite attaches, causing a loss of microvilli, inflammation, and subsequent malabsorption and enhanced secretion. As few as 10–30 ingested oocysts can cause infection that can persist in an individual because of repeated life cycles within the gastrointestinal tract (Reference 15). Oocysts are shed in feces for up to 2 months after diarrhea subsides and are infectious immediately upon excretion (Reference 14). Although some infections may be asymptomatic, most individuals have profuse, watery diarrhea that contains mucus and lasts for about 2 weeks. Nausea, vomiting, and abdominal cramping may accompany the diarrhea, and fever may also be present. Patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) can have a severe, cholera-like presentation that can persist for the patient's lifetime. Diagnosis of cryptosporidiosis is made when oocysts are identified on acid-fast staining of stool or when stool antigens are identified through immunoassay techniques.

Treatment of cryptosporidiosis does not routinely eradicate the infection, particularly in immunocompromised hosts. Immunocompetent individuals and those who are asymptomatic generally do not need antimicrobial therapy because the infection is self-limiting. Nitazoxanide (100 mg orally twice daily for 3 days) may be considered for treatment of malnourished immunocompetent children with prolonged diarrhea because it has been shown to induce a positive parasitologic response and reduction in diarrhea (References 16, 17). Nitazoxanide has a unique mechanism of action involving interference with anaerobic energy metabolism through the disruption of electron transport, and it is not associated with any significant adverse effects. Optimal therapy in patients with HIV/AIDS is to restore immune function through the use of highly active antiretroviral therapy; if this is not possible or if it fails, antimicrobial and antidiarrheal therapies are recommended (Reference 15). Paromomycin, azithromycin, and nitazoxanide have been used but are only modestly effective in this population because of a sustained immunodeficient state.

Efforts to control cryptosporidiosis are best aimed at preventing oocyst transmission. Oocysts are resistant to many disinfectants and antiseptics, including chlorine, alcohol, and alkaline chemicals (Reference 14). Severely immunocompromised patients should avoid water from lakes or streams and contact with young animals, and all water should be boiled before consumption (Reference 15). All individuals should practice proper hygiene to prevent the spread and ingestion of oocysts and avoid swallowing water from swimming pools, lakes, ponds, streams, or other untreated water sources.

Bacterial Causes of Infectious Diarrhea

Bacterial causes of infectious diarrhea are less common than viral causes, but their associated syndromes are well characterized. Two main categories of infection occur: enterotoxigenic (or watery diarrhea) and dysentery (or invasive diarrhea). Enterotoxigenic diarrhea is often self-limiting, whereas dysentery requires close monitoring of patients who have fever with stools containing blood and pus. Bacterial diarrhea is more common in summer months, whereas viral diarrhea is more common in winter and spring. Antibiotic therapy, outlined in Table 2, may be indicated for certain infections.

Shigellosis

Shigellosis, or bacillary dysentery, is a common cause of mortality from diarrhea. It affects around 165 million people worldwide, mostly children, and leads to more than 1 million deaths, 60% of which are in children younger than 5 years (References 18, 19). In the United States, 450,000 people are infected annually, with most cases caused by person-to-person transmission in day care centers and crowded living areas (Reference 18). Transmission occurs easily, requiring as few as 10–100 organisms to cause infection after ingestion (Reference 19). Shigellosis can also be spread through contaminated food and water, leading to large outbreaks.

S*higella* spp. are nonmotile, gram-negative bacilli in the Enterobacteriaceae family. The four species most commonly associated with disease are *Shigella dysenteriae* type 1, *Shigella flexneri*, *Shigella boydii*, and *Shigella sonnei*. The most common species in the United States are *S. sonnei* and *S. flexneri*. After ingestion, bacterial replication and spread occur within intestinal epithelial cells and bowel mucosa and submucosa, leading to inflammation, ulceration, tissue sloughing, and bloody mucosal exudates. The entire colon is usually involved, but the infection seldom spreads to the bloodstream; bacteremia is more likely in malnourished and immunocompromised children. *S. dysenteriae* type 1 produces Shiga toxin, a virulence factor that causes more severe disease, and is associated with complications such as toxic megacolon and hemolytic-uremic syndrome (HUS). This syndrome is characterized by hemolytic anemia, thrombocytopenia, and renal failure; although rare, HUS can be fatal. Diagnosis of shigellosis is made after the development of dysentery and is confirmed by stool culture or PCR.

Shigellosis usually follows a biphasic pattern, with initial signs and symptoms including abdominal pain and cramping, fever, and frequent watery diarrhea. Within 48 hours, severe abdominal pain and tenderness develop, followed by bloody diarrhea and tenesmus, or a feeling of incomplete defecation with rectal pain. Fluid and electrolyte losses can be severe in infants and young children. If left

Table 2. Antibiotic Therapy for Bacterial Infectious Diarrhea in Children

Infection Type	Indications for Antibiotics	Antibiotic Regimens	Considerations
Shigellosis	Severe infection, immunocompromised, malnourished, day care attendance	Azithromycin 10 mg/kg/day orally × 3 days	Resistance rates unknown because of lack of reliable testing
		Ciprofloxacin 10–15 mg/kg twice daily orally × 3–5 days	Reserve for cases of multidrug resistance
		Ceftriaxone 50 mg/kg once daily intramuscularly × 2–5 days	Must be given parenterally; reaches gastrointestinal tract because of biliary excretion
Salmonellosis			
Gastroenteritis	Infants younger than 3 months, immunocompromised, hemoglobinopathies, malignancies, chronic gastrointestinal diseases	Trimethoprim/sulfamethoxazole 4–5 mg/kg (of trimethoprim) orally twice daily × 5 days	Avoid in children younger than 2 months; increased risk of kernicterus
		Ampicillin 25 mg/kg orally four times/day × 5 days	Local resistance rates to ampicillin may be high
Enteric (typhoid) fever, uncomplicated	All patients	Azithromycin 20 mg/kg orally once daily × 5–7 days	Resistance rates unknown because of lack of reliable testing
		Ceftriaxone 75 mg/kg intravenously once daily × 5–7 days	
Complicated enteric fever, extraintestinal infection	All patients	Ceftriaxone 75 mg/kg intravenously once daily × 10–14 days (4–6 weeks if endovascular infection, osteomyelitis, or meningitis)	Ampicillin can be used if isolate is susceptible
Enterotoxigenic *Escherichia coli*	Moderate to severe diarrhea	Azithromycin 10 mg/kg/day orally × 1–3 days	Drug of choice for children
		Rifaximin 200 mg three times/day orally × 3 days	Indicated only for children 12 years and older
Campylobacteriosis	Severe bloody stools, elevated temperature, prolonged illness, pregnancy, immunocompromised	Azithromycin 20–30 mg/kg/day orally × 1 dose or 10 mg/kg/day orally × 3 days	Drug of choice
Cholera	Severe infection	Doxycycline 4 mg/kg orally once	Avoid in children younger than 8 years because of effects on tooth formation and bone growth
		Azithromycin 20 mg/kg orally once	
Clostridium difficile infection	Moderate illness or mild-moderate illness that persists after discontinuing antibiotic therapy	Metronidazole 7.5 mg/kg orally four times/day × 10–14 days	Drug of choice; can be given intravenously if oral administration is not an option
	Severe illness or failure of metronidazole	Vancomycin 10 mg/kg orally four times/day × 10–14 days	Reserved for severe illness because of high cost and concern for vancomycin resistance emergence

untreated, shigellosis lasts about 1 week, but organisms can be excreted for up to 30 days after illness onset (Reference 19). Complications that are more common in children include rectal prolapse, seizures, and malnutrition.

Shigellosis is generally self-limiting and may require fluid replacement therapy if dehydration becomes significant. Antibiotic therapy is usually not indicated unless the infection is severe or occurs in a child who attends day care, is immunocompromised, or is malnourished. Antibiotics shorten the duration of diarrhea and reduce infectivity by minimizing fecal shedding; however, antimicrobial resistance among *Shigella* is a growing concern and is well documented worldwide (Reference 19). Nationwide, more than 60% of strains are resistant to ampicillin, and more than 40% are resistant to trimethoprim/sulfamethoxazole; however, there is minimal resistance to ceftriaxone and fluoroquinolones (Reference 20). Higher resistance rates may occur in certain geographic locations, so clinicians should request culture and susceptibility results when antibiotic therapy is indicated (Reference 21). Empiric antibiotic regimens for shigellosis in children can be found in Table 2. Azithromycin is the empiric drug of choice, but susceptibility breakpoints have not been established by the Clinical and Laboratory Standards Institute, so detection of resistance is not routinely identified (Reference 21). Ciprofloxacin should be reserved for cases of multidrug resistance, and parenteral ceftriaxone can be given to children who are unable to tolerate oral antibiotics (Reference 22). If susceptible, ampicillin or trimethoprim/sulfamethoxazole can be used. Antimotility agents are not recommended for shigellosis because they can worsen dysentery and increase the risk of complications such as toxic megacolon.

Preventing the spread of shigellosis is important to minimize outbreaks. Control measures should include strict hand hygiene, proper food cooking and storage, avoidance of recreational water or day care attendance for at least 1 week after diarrhea resolution, exclusion of infected individuals from handling food, and preventing child care workers from preparing food if they change diapers. No vaccines are currently available for preventing shigellosis.

Salmonellosis

Salmonellosis is a common foodborne illness in the United States, in which nontyphoidal strains cause more than 1 million infections annually, leading to 16,000 hospitalizations and 600 deaths (Reference 23). The incidence is highest in children younger than 1 year, which may be related to their reduced gastric acidity, gut immaturity, or underdeveloped immune systems (Reference 24). Outbreaks are associated with contaminated food or water, but fecal-oral transmission is also likely in children. Infection typically results from the ingestion of contaminated vegetables or fruits; undercooked pork, poultry, or beef; or unpasteurized dairy products. Accounting for up to 5% of cases, exotic pets including snakes, turtles, and iguanas are also an important source of infection because they are often carriers of *Salmonella* in their gastrointestinal tracts.

Salmonella enterica are motile, gram-negative bacilli in the Enterobacteriaceae family. Serotypes Typhi and Paratyphi are the most prevalent worldwide and cause enteric fever, or typhoid, from bacteremia. The nontyphoidal strains, serotypes Typhimurium and Enteritidis, are most common in the United States and primarily cause gastroenteritis, but they can lead to bacteremia and localized extraintestinal infections. The infectious dose of *Salmonella* (around 1 million organisms) is higher than with *Shigella* but is lower in people with reduced gastric acidity. Once ingested, the organisms penetrate the epithelial lining of the distal ileum and colon, causing inflammation, tissue damage, and fluid secretion across the intestinal mucosa. In certain individuals or with certain serotypes, bacteremia may occur after translocation through the intestinal wall and can lead to localized extraintestinal infections in areas such as bone, heart, central nervous system, or spleen. Diagnosis of salmonellosis is made upon isolating the organism from the stool in patients with gastroenteritis, or from blood or bone marrow in those with enteric fever. Recovery of *Salmonella* from stool is most likely early in the course of illness, but bacteria may continue to be shed for up to 12 weeks in children (Reference 25). About 1% of infected individuals become chronic carriers and shed organisms for more than 12 months because of biliary tract carriage (Reference 25).

Clinical manifestations of salmonellosis depend on the infecting serotype and the host. After the ingestion of nontyphoidal *Salmonella*, symptoms typically occur within 72 hours. Most patients experience nausea, vomiting, and abdominal cramping, followed by fever, headache, and diarrhea that is usually nonbloody. Gastroenteritis is often self-limiting and resolves in 3–7 days. Invasive disease and extraintestinal infections are more likely in infants younger than 3 months and in children with immunodeficiencies, malignancy, sickle-cell disease, or inflammatory bowel disease. After typhoidal strains are ingested, fever and nonspecific systemic symptoms, including profuse sweating, headache, chills, anorexia, myalgias, and malaise, develop within 5–21 days. Diarrhea may be present in enteric fever, and sequelae such as intestinal bleeding or perforation, delirium, or hepatosplenomegaly can develop within 3 weeks of illness onset. *Salmonella* infection can also be asymptomatic, leading to a chronic carrier state.

Treatment of *Salmonella* infection depends on the clinical severity and host. Most cases of gastroenteritis do not require antibiotics, and their use may result in prolonged fecal shedding and a higher rate of chronic carriage. Supportive treatment with ORT is usually beneficial. Antibiotics are recommended for high-risk patients with nontyphoidal *Salmonella* infection: children

younger than 3 months or those with immunodeficiencies, hemoglobinopathies, malignancy, or chronic gastrointestinal tract disease (Reference 25). For typhoid fever and invasive *Salmonella* infections, antibiotic therapy is warranted. Empiric regimens for salmonellosis, found in Table 2, should consider geographic resistance patterns. Typhoidal strains, which tend to be more drug resistant, should be treated empirically with broad-spectrum agents (Reference 20). Culture and susceptibility results should be used to minimize broad-spectrum antibiotic use and to monitor for drug-resistant strains. On the basis of susceptibility testing, children who are chronic carriers should be treated with an antibiotic such as amoxicillin or trimethoprim/sulfamethoxazole for 3 months to eradicate the carrier state that promotes spread to others.

Salmonella infection can be prevented with a variety of approaches. These methods include meticulous hand hygiene, sanitary food preparation and water supplies, and sanitary sewage and waste disposal, as well as excluding infected individuals from handling food or attending day care. Children younger than 5 years and immunocompromised patients should avoid contact with reptiles and rodents. Eggs and meat should be cooked thoroughly, and foods containing raw eggs should not be ingested. Breastfeeding is protective against infantile salmonellosis because it provides passive immunity and limits exposure to potentially contaminated formula or water. Typhoid fever can be prevented through vaccination using one of two typhoid vaccines: an oral live-attenuated vaccine or an injectable capsular polysaccharide vaccine. Vaccination is recommended for children who are traveling to an endemic area such as Africa, Asia, or Latin America or who are household contacts of chronic carriers. The oral vaccine can be given to children 6 years and older (four doses given every other day), whereas the injectable vaccine can be used in children as young as 2 years (a single dose). The oral vaccine should not be used in children who are immunocompromised or who have an active gastrointestinal tract illness.

E. coli

Infectious diarrhea caused by *E. coli* is categorized on the basis of pathogenic characteristics. Enterotoxigenic *E. coli* (ETEC) is the most common form of *E. coli* diarrhea worldwide, with around 80,000 cases occurring annually in the United States mainly from international travel (Reference 26). Enterotoxigenic *E. coli* causes watery diarrhea and is associated with foodborne outbreaks and traveler's diarrhea in areas where sanitation is inadequate. Person-to-person transmission is uncommon because infection requires a relatively large inoculum. In contrast, enterohemorrhagic *E. coli* (EHEC) causes bloody diarrhea, which can result in hemorrhagic colitis, HUS, and potentially death. Interpersonal spread occurs easily with EHEC because ingestion of only a few organisms can lead to infection. In the United States, EHEC is often caused by *E. coli* 0157:H7. Outbreaks of EHEC are associated with contaminated beef or vegetables, unpasteurized dairy products or apple cider, and exposure to animals in petting zoos. Enteroinvasive *E. coli* (EIEC) and enteropathogenic *E. coli* (EPEC) occur mainly in children in developing countries. Enteroaggregative *E. coli* (EAEC) is common in HIV infection and usually leads to persistent watery diarrhea.

E. coli is a gram-negative bacillus found in the intestinal tract of humans, cattle, deer, and other farm animals. Gastrointestinal damage from *E. coli* infection varies depending on the infecting organism. Enterotoxigenic *E. coli* have the ability to produce cholera-like enterotoxins that cause profuse secretory diarrhea. Enterohemorrhagic *E. coli* produces Shiga-like toxins that disrupt large intestinal mucosa, creating bloody diarrhea. These toxins can invade the bloodstream and damage the vascular supply to the gastrointestinal tract and kidneys, resulting in HUS. Enteroinvasive *E. coli* resemble *Shigella* and cause intestinal damage and symptoms similar to dysentery. Enteropathogenic *E. coli* adhere to intestinal epithelial cells, which disrupts their integrity, leading to watery diarrhea. Enteroaggregative *E. coli* adhere to mucosal cells in a biofilm layer that causes persistent colonization, epithelial damage, and watery diarrhea. Diagnosis of *E. coli* diarrhea is complicated by the inability to differentiate between normal *E. coli* stool flora and diarrhea-associated strains. *E. coli* 0157:H7 can be detected by its inability to ferment sorbitol, followed by subsequent serotyping. Shiga-like toxins from EHEC can be detected with immunologic assays.

Clinical presentation of *E. coli* diarrhea manifests in different ways. Enterotoxigenic *E. coli* and other nonhemorrhagic strains cause abrupt watery diarrhea, nausea, and abdominal cramping that usually resolve in 24–48 hours. Enteropathogenic *E. coli* often cause low-grade fever and vomiting, whereas EAEC diarrhea is persistent and watery with minimal or no vomiting. Enteroinvasive *E. coli* can present with dysentery symptoms of bloody diarrhea that contains mucus and pus, tenesmus, and fever. Enterohemorrhagic *E. coli* is associated with severe symptoms that begin as abdominal cramping and distension, watery diarrhea, and nausea or vomiting but then progress to bloody diarrhea, with increased abdominal pain within 48 hours. Fever is not a common feature of EHEC. Although most cases resolve after 1 week, HUS can develop in up to 10% of patients with EHEC and is most common in children between 1 and 5 years of age (Reference 27).

All forms of *E. coli* diarrhea should be managed with fluid and electrolyte therapy to prevent dehydration. Enterohemorrhagic *E. coli* should not be treated with antibiotics because they may increase the release of toxins upon bacterial lysis, increasing the risk of HUS

(Reference 28). Antimotility agents should also not be used in EHEC because they can reduce the clearance of the organisms and toxins. For other forms of *E. coli* diarrhea, particularly those associated with travel, antibiotics may be considered for moderate to severe diarrhea, but antimicrobial resistance can affect treatment success. Table 2 lists empiric agents that can be considered. Loperamide can reduce the severity of ETEC, but bismuth subsalicylate should be avoided because of the risk of Reye syndrome in children.

Preventing *E. coli* infection focuses on the avoidance of contaminated food and water sources. Methods to prevent infection include proper cooking of ground beef, ingestion of only pasteurized milk or apple juice, and avoidance of tap water, uncooked or unpeeled foods, and inadequately stored foods during travel to developing countries. Use of proper hand hygiene and exclusion of symptomatic individuals from day care centers and recreational water sources are also helpful to prevent spread of infection. No vaccines are currently available to prevent *E. coli* infection.

Campylobacteriosis

Campylobacteriosis is the most common bacterial cause of infectious diarrhea, accounting for up to 2.5 million cases annually in the United States (Reference 23). The two peak age groups for infection are children younger than 1 year and individuals between 15 and 44 years of age, and males are infected more commonly. Infection is transmitted through contaminated food or water and is often associated with poultry consumption. Risk factors for campylobacteriosis include exposure to chickens, other birds, or cats; consumption of undercooked poultry or other meats, unpasteurized milk, or contaminated water; international travel; and recent antimicrobial use.

Campylobacter spp. are motile, curved, gram-negative bacilli that are sensitive to gastric acid. The two most common species to cause diarrhea are *Campylobacter jejuni* and *Campylobacter coli*. Infectious doses are about 800 organisms but are lower in individuals with reduced gastric acidity. After ingestion, replication occurs in the small intestine, and organisms adhere to intestinal tissue in the jejunum, ileum, colon, and rectum, leading to local inflammation. Some strains of *C. jejuni* produce enterotoxins or cytotoxins that contribute to pathogenicity (Reference 29). Host immunity plays a role in the development of campylobacteriosis, and frequent exposure provides short-term protection against infection but not colonization (Reference 30). Diagnosis of campylobacteriosis is confirmed with stool culture or enzyme immunoassay.

Common clinical manifestations of campylobacteriosis occur within 1–7 days of ingestion and include fever, abdominal cramps, and diarrhea, which can be either watery or bloody. Dysentery occurs in around one-half of cases. Fever, headache, myalgia, and malaise can also be present. Some patients may experience only abdominal pain with minimal diarrhea. Gastrointestinal symptoms usually resolve within 1 week or less. Extraintestinal infections may occur and are more common in immunocompromised children and neonates; these include sepsis, septic arthritis, meningitis, pancreatitis, cholecystitis, and osteomyelitis. Campylobacteriosis leads to about 30% of Guillain-Barré syndrome (GBS) cases, which occur within 3 weeks of infection, but the risk of developing GBS is less than 1 case per 1,000 *C. jejuni* infections (Reference 31).

The cornerstone of treatment of campylobacteriosis is ORT for hydration and electrolyte replacement. Antibiotics are usually unnecessary; they do not reduce illness duration or severity unless given within 4 days of symptom onset, but they can shorten the duration of bacterial shedding. Antibiotics should be considered in patients with severe bloody stools, elevated temperature, prolonged illness for longer than 1 week, pregnancy, and immunocompromised states (see Table 2). Macrolides are the agents of choice because of increasing fluoroquinolone resistance from overuse in enteric infections and use of fluoroquinolones in poultry. Severely ill children can be treated with intravenous gentamicin. Antimotility agents should be avoided because they prolong the duration of infection and enhance toxin retention.

Prevention of campylobacteriosis focuses on hand hygiene and avoiding contaminated food and water. Individuals should wash their hands, all utensils, and cutting boards after contact with uncooked poultry and avoid cross-contamination of vegetables and other foods with raw poultry juices. All poultry should be cooked thoroughly before eating. Hand hygiene is also important after defecation and contact with animal feces. Infected individuals should be excluded from food preparation and day care. No vaccine is currently available to prevent *Campylobacter* infection.

Cholera

Cholera is uncommon in the United States but is endemic in areas of South Asia. Some strains cause pandemics, which have been reported mainly in parts of Africa and South America. Cholera causes loss of large volumes of watery stool, severe dehydration, and shock. It is transmitted through water or contaminated foods, especially undercooked shellfish or fish. Cholera grows well in warm temperatures and appears in moist grains stored at ambient temperatures. The infectious dose from environmental sources is around 10^{10} organisms but is lower in those with reduced gastric acidity. Risk factors for cholera include the ingestion of undercooked seafood, low gastric acidity, and blood type O (Reference 32).

Vibrio cholerae is a motile gram-negative bacillus similar to Enterobacteriaceae, with several serogroups known to cause pandemics. Infection occurs when organisms colonize the small intestine after ingestion and penetrate the mucosal layer. Enterotoxin production is an important pathogenic feature of cholera that leads to excessive isotonic fluid loss in the small intestine, exceeding colonic absorptive capacity. Electrolyte-rich watery diarrhea develops, which is highly infectious and allows for person-to-person spread. Diagnosis is made upon request for isolation of vibrios from stool, which can be further serotyped at state laboratories.

Cholera occurs within a few hours to 5 days after ingestion. It is characterized by an abrupt onset of painless watery diarrhea and often vomiting. Stools are typically of large volume, reaching a loss of 1 L/hour, and have the consistency of rice water. Complications of cholera include hypoglycemia, seizures, renal failure, and mental status changes. Severe muscle cramps are common from electrolyte imbalances. Severe dehydration, metabolic acidosis, and shock occur rapidly and can progress to death within hours if untreated.

Rapid treatment of cholera with ORS is vital to replace fluids and electrolytes and thus prevent shock. Rice-based ORS is preferred because it is more effective than glucose-based ORS in reducing stool output and because it reduces overall fluid requirements (Reference 33). Intravenous rehydration with lactated Ringer's solution may need to be given before ORS if shock is present. Antibiotics should be given to children with severe disease because they can shorten the duration of diarrhea and reduce fluid loss (Table 2). Antibiotic resistance is common among endemic strains and should be monitored during outbreaks to ensure proper treatment is provided.

Prevention of cholera focuses on ensuring a safe water supply through proper sanitation, thorough cooking of seafood, and appropriate hand hygiene after defecation and before food preparation. Antibiotic prophylaxis for household contacts is not recommended because of resistance concerns. Two oral vaccines are available in other countries but not in the United States. Vaccination is not recommended for most travelers to endemic areas because the risk of infection is low, and the immunity provided by the vaccines is incomplete.

Clostridium difficile Infection

C. difficile is the most common cause of nosocomial infectious diarrhea in the United States. Both the incidence of community-acquired disease and severe infection is increasing, and outbreaks from a single strain (North American pulsed-field type 1, or NAP-1) have emerged in recent years. *C. difficile* infection (CDI) is most common in adults, but the prevalence is increasing in children (Reference 34). Pediatric risk factors for CDI include solid-organ transplantation, presence of a gastrostomy or jejunostomy tube, recent receipt of fluoroquinolone and other broad-spectrum antibiotics, inflammatory bowel disease, lack of previous hospitalization, and proton pump inhibitor or histamine-2 receptor antagonist therapy (References 34–36).

C. difficile is a gram-positive, spore-forming anaerobic bacillus that causes a toxin-mediated diarrhea. Infection occurs after the ingestion of organisms or spores that can survive harsh environmental conditions and are resistant to disinfectants, including alcohol. Ingested spores germinate in the small intestine and travel to the colon, where they can produce toxins A and B, which are responsible for disease. Toxin A, an enterotoxin, causes fluid and mucus secretion, mucosal damage, and inflammation, whereas toxin B, a cytotoxin, is more potent and causes mucosal damage. Pseudomembranous plaques form in the colon and enlarge with disease progression to affect the entire colon and rectum. Diagnosis of CDI is made by detecting toxin A or B in the stool of symptomatic individuals. Endoscopy may be needed to diagnose CDI in individuals with an ileus.

C. difficile infection varies in severity from mild diarrhea to life-threatening pseudomembranous colitis and toxic megacolon. For antibiotic-associated infections, CDI can occur on the first day of antibiotic therapy or as late as several weeks after completing antibiotics. Diarrhea is usually watery and can be mild with only a few loose stools per day, accompanied by abdominal pain, low-grade fever, and mild leukocytosis. Colitis is characterized by frequent watery diarrhea with up to 15 bowel movements per day, abdominal pain and distension, nausea, anorexia, fever, and leukocytosis. Fulminant disease involves severe abdominal pain, profuse diarrhea, elevated temperature, dehydration, tachycardia, marked leukocytosis, and possibly hypotension. Some patients develop pseudomembranous colitis or an ileus. Toxic megacolon can develop with acute colonic dilation, signs of systemic disease (elevated temperature, tachycardia, hypotension), and cessation of bowel movements. Mortality is high if toxic megacolon develops. Some patients are asymptomatic carriers of *C. difficile*, which has been noted in up to 70% of infants (Reference 37).

Initial treatment of CDI should include halting antibiotic therapy when possible. Although some patients may respond to discontinuing antibiotics alone, antimicrobial therapy directed at *C. difficile* is recommended for most cases (Table 2). Oral metronidazole and oral vancomycin have similar efficacy in mild illness, but vancomycin is preferred in severe illness. In patients who cannot receive oral therapy, intravenous vancomycin cannot be used because it does not achieve adequate concentrations in the gut; in these patients, intravenous metronidazole can be used with or without vancomycin enema, which is useful in cases of peristaltic ileus. Recurrent CDI occurs in about 20% of patients within 2–3 weeks of discontinuing treatment. Another course of the initial antibiotic is recommended in recurrent disease; relapse is not associated with antibiotic

resistance, but rather, failure to eradicate spores or reinfection from an environmental source. Newer antibiotics including fidaxomicin and nitazoxanide, which have been studied for CDI, may result in fewer recurrences, but their place in therapy is yet to be defined. Children with several relapses are difficult to manage; treatment options to consider are vancomycin pulse dosing, vancomycin tapers, intravenous immune globulin, or fecal bacteriotherapy (Reference 38). Adjunctive therapies for CDI, including cholestyramine and probiotics, have not consistently been proved beneficial. Antiperistaltic agents are contraindicated because they increase the risk of toxic megacolon, which often requires surgical intervention.

Measures to prevent *C. difficile* transmission focus on proper infection control methods. Handwashing with soap and water is necessary to prevent spread because alcohol-based products are not effective at eliminating spores. Health care providers should use contact precautions and wear gowns and gloves while caring for *C. difficile*–infected patients. Isolating infected patients should also be practiced in institutional settings. Chlorine-containing cleaners at a concentration of at least 1000 parts per million are effective in minimizing environmental contamination. Infected individuals should be excluded from day care settings until diarrhea subsides.

Traveler's Diarrhea

Traveler's diarrhea occurs when people travel from industrialized nations to developing countries and consume contaminated water or food. Children with traveler's diarrhea are often infected with ETEC; *Campylobacter*, *Salmonella*, or *Shigella* spp.; or rotavirus. Risk factors for developing traveler's diarrhea include ingesting tap water, uncooked foods, and foods that are stored inadequately, such as buffet-style meals. Most cases occur within 2 weeks of travel and resolve in a few days. Typical signs and symptoms are malaise, nausea, anorexia, abdominal cramps, and mild to moderate diarrhea that can interfere with planned activities. Traveler's diarrhea is rarely life threatening.

Treatment focuses on avoiding dehydration with the use of ORS and returning to functional status as soon as possible. Antibiotics, which can reduce the duration of diarrhea, should be considered in children having diarrhea for longer than 24 hours (Reference 39). Azithromycin 10 mg/kg/day for 3 days is recommended for treating children instead of fluoroquinolones, which are typically used in adults (References 39, 40). In children 12 years and older, rifaximin is an alternative agent for use in travelers to Mexico or Jamaica, where *E. coli* is predominant. Antimotility agents are not recommended unless they are administered with antibiotics.

Prevention of traveler's diarrhea focuses on education and avoidance of high-risk foods and beverages. Antibiotic prophylaxis is not recommended because of antimicrobial resistance concerns. Bismuth subsalicylate taken four times/day for up to 3 weeks may inhibit enterotoxin activity, but it should not be used in children because of the risk of Reye syndrome. Probiotics may minimize infection from pathogenic organisms, but more studies are needed before they can be routinely recommended (Reference 39).

Conclusions

Infectious diarrhea in children, which is caused by a variety of microorganisms, can result in significant dehydration and electrolyte disturbances. Although a large proportion of cases occur in developing countries, children in the United States are also susceptible because of contaminated food and water sources and international travel. Treatment should always involve rehydration, preferably with ORS, and antibiotics when appropriate. Knowledge regarding infectious sources and proper hygiene is vital to limiting the spread of infectious diarrhea.

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CHAPTER 39

Urinary Tract Infections in Children

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Learning Objectives

1. Identify risk factors for the development of urinary tract infections (UTIs) in children.
2. Recognize the uropathogens and their mechanisms of entry into the urinary tract to cause infection.
3. Describe UTI classification systems, signs and symptoms, and diagnostic criteria in children.
4. Review the pharmacotherapeutic options employed in the treatment of pediatric UTIs.
5. Monitor pediatric UTI patients for drug efficacy and toxicity.

Abbreviations in This Chapter

CFU	Colony-forming unit(s)
LE	Leukocyte esterase
SPA	Suprapubic aspiration
US	Ultrasonography
UTI	Urinary tract infection
VCUG	Voiding cystourethrography
VUR	Vesicoureteral reflux
WBC	White blood cell

Introduction

The urinary tract consists of the kidneys, ureters, bladder, and urethra. A urinary tract infection (UTI) occurs when pathogenic organisms infect any of the structural components of the urinary tract. Urinary tract infections are common in the pediatric population, leading to acute morbidity and potentially chronic medical sequelae, which include recurrent infections, acute renal injury, and potentially end-stage renal disease, which leads to hypertension, dialysis, and/or renal transplantation (Reference 1). Appropriate management of the pediatric UTI patient is directed at minimizing the risk for renal damage.

Epidemiology

The overall incidence of UTIs in prepubertal children is reported to be 3% for females and 1% for males. However, UTI incidence varies with patient age and sex and, in males, whether the patient is circumcised. The incidence of UTI in females younger than 12 months ranges from 0.4% to 1%, whereas the rate is 0.188% in circumcised and 0.702% in uncircumcised boys in this age group. In preschool children (1–5 years of age), the UTI incidence for girls is 0.9% to 1.4% and for boys, 0.1% to 0.2%. For school-aged children, there is a 0.7% to 2.3% incidence in females and a 0.04% to 0.2% incidence in males (References 1, 2).

Urinary tract infection prevalence is higher in children 12 months and younger who present with fever. One meta-analysis reported the UTI prevalence rates for girls as 7.5%, 5.7%, and 8.3% and for boys as 8.7%, 3.3%, and 1.7% for children younger than 3 months, 3–6 months, and 6–12 months, respectively. The prevalence varies significantly depending on the circumcision status of the males. The reported UTI prevalence for boys younger than 3 months is 2.4% if circumcised and 20.1% if uncircumcised. Urinary tract infection prevalence rate for boys 6–12 months of age is 0.3% if circumcised and 7.3% if uncircumcised. Mean UTI prevalence for pediatric patients younger than 19 years presenting with urinary symptoms and/or fever is reported as 7.8% overall in this meta-analysis (Reference 3).

Etiology

The most common pathogens causing UTI are bacteria of enteric origin. *Escherichia coli,* a gram-negative rod, is the most prevalent pathogen, accounting for more than 80% of pediatric UTIs (References 4, 5). Other, less frequently isolated gram-negative urinary pathogens include *Citrobacter* spp., *Enterobacter* spp., *Klebsiella* spp., *Morganella morganii, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, Serratia* spp., and *Neisseria gonorrhea* (Reference 1). Gram-positive organisms that cause UTIs in children include *Enterococcus* spp., *Staphylococcus aureus, Staphylococcus saprophyticus, Staphylococcus epidermidis,* and group B and D streptococci (Reference 1). Less common uropathogens in children include *Candida albicans, Chlamydia trachomatis, Ureaplasma urealyticum, Mycoplasma hominis,* and adenoviruses (Reference 6).

Pathogenesis

The primary host defense mechanism against UTI is the continuous urine flow from the kidneys to the bladder, ultimately resulting in micturition and complete bladder emptying through the urethra. Normal urinary flow typically clears urinary tract pathogens. In addition, several antibacterial inhibitory factors in urine play protective

roles against UTIs. Inhibitory substances in urine include urea, organic acids, and salts. Urine pH and osmolarity also contribute to antibacterial activity. Low osmolarity inhibits bacterial growth; high osmolarity, if associated with low pH, is also inhibitory. Other substances that inhibit bacterial adherence to urinary tract mucosa include the Tamm-Horsfall protein, bladder mucopolysaccharide, low-molecular-weight oligosaccharides, secretory immunoglobulin A, and lactoferrin. The inflammatory response (e.g., polymorphonuclear neutrophils, cytokines) as well as humoral and cell-mediated immunity are other components involved in the urinary tract's host defense mechanism against invading pathogens (References 1, 4, 7). Specific host factors increase susceptibility to bacteriuria (References 1, 4, 7, 8). Table 1 summarizes the host factors and proposed mechanism of these factors in increasing the risk of UTI.

Bacterial factors also influence susceptibility to infection. Not all strains of bacterial species identified as UTI pathogens are capable of infecting the urinary tract. Specific virulence factors are necessary for bacteria to colonize cells of the urinary tract and facilitate ascension into the bladder (and potentially into the upper urinary tract) while evading the host defense mechanisms. Adhesins such as type 1 fimbriae and P fimbriae, which are commonly present in uropathogenic bacteria, promote urinary tract colonization. Type 1 fimbriae bind to mannose-containing receptors and are often found in *E. coli* strains that cause acute cystitis. Conversely, P fimbriae are mannose-resistant, and P fimbriated *E. coli* are strongly associated with acute pyelonephritis. After attachment to the uroepithelial mucosal surface, additional virulence factors (e.g., ureases, iron-scavenging proteins, α-hemolysin, bacterial toxins) are produced to support continued bacterial growth within the urinary tract (Reference 4).

Table 1. Host Factors Associated with Increased Risk of UTIs in Children (References 1, 4, 7, 8)

Host Risk Factor	Proposed Mechanism/Supporting Observations
Younger age group (neonates and infants)	Incompletely developed immune system
	Breastfeeding may be protective by supplementing maternal IgA, lactoferrin, and anti-adhesive oligosaccharides.
Female sex	Periurethral and vaginal moisture promotes uropathogen growth.
	Shorter urethra increases probability of ascending infection.
Uncircumcised infants	Increased concentration of uropathogens in boys with foreskin
Fecal and perineal colonization	Colon and urogenital flora expressing specific virulence factors
	Antibiotic exposure may alter microflora, possibly resulting in more resistant microbial strains.
Constipation	Rectum chronically dilated by feces, leading to voiding dysfunction
Anatomic anomalies (e.g., posterior urethral valves, vesicoureteral reflux)	Inadequate clearance of uropathogens
	Surgical intervention may be required.
Functional abnormalities (e.g., neurogenic bladder)	Urinary retention, urinary stasis, and incomplete bladder emptying result in decreased urinary bacterial clearance.
Female sexual activity	Bowel and vaginal bacterial transfer to urethral meatus, leading to postcoital bacteriuria.
Spermicide use	Alteration of vaginal flora facilitating adherence of *Escherichia coli* to epithelial cells
HIV disease	Immunocompromised state
Renal transplantation	Immunocompromised state
Diabetes mellitus	Urine glucose supplies a growth medium for pathogens.
Genetic predisposition	White females are more likely to develop a UTI than their African American counterparts.
	Associations between specific blood group phenotypes and recurrent UTIs have been reported.
	Host cell receptors facilitating bacterial adherence to uroepithelium (e.g., **α**-Gal(14) **β**-Gal receptor) have been identified.

HIV = human immunodeficiency virus; IgA = immunoglobulin A; UTI = urinary tract infection.

Infection Pathways

Infection of the urinary tract typically occurs by one of four pathways. The most common pathway is retrograde ascent. Uropathogens associated with retrograde ascent usually originate from the host's gastrointestinal tract and colonize vaginal or periurethral areas. Vaginal flora may also serve as a reservoir for organisms causing UTIs. The pathogens enter the urinary tract through the urethra and migrate to the bladder, where they multiply and potentially progress to infect the upper urinary tract (i.e., kidney) (References 1, 7).

A second UTI pathway is nosocomial infection. Introduction of a foreign body or instrumentation (e.g., urethral catheterization) into the urinary tract increases the risk of UTI, particularly with longer durations of catheterization (References 1, 4). Nosocomial UTIs are associated with more resistant pathogens such as *Pseudomonas, Enterobacter, Citrobacter, Proteus, Providencia,* or *Enterococcus* spp. Candidal infections may also occur in catheterized children (Reference 8).

A third pathway for infection is the hematogenous route. The infecting organism originates from a nidus outside the urinary tract. The organism disseminates from its original nidus, resulting in a systemic infection with subsequent urinary tract seeding (e.g., staphylococcal bacteremia or endocarditis, neonatal sepsis) (Reference 6). This pathway is more common in infants and immunocompromised patients (References 1, 4). Finally, a fourth pathway of infection involves the development of a fistula between the urinary tract and the gastrointestinal tract or vagina (e.g., vesicointestinal, urethrorectal, or vesicovaginal fistulae). This mechanism is seldom encountered (Reference 1).

Classification

There are several classification methods for UTIs. One method is based on the infection site. For example, the infection site may be in the bladder (cystitis), urethra (urethritis), urine (bacteriuria), or kidney (pyelonephritis). The infection site in the urinary tract may be more broadly classified as a lower or upper UTI. Cystitis and urethritis are examples of lower UTIs, whereas pyelonephritis is classified as an upper UTI (References 1, 2, 9).

A second method classifies UTIs as either complicated or uncomplicated. A complicated UTI describes genitourinary tracts with structural or functional abnormalities; it also includes UTIs attributed to instrumentation such as indwelling catheters. An uncomplicated UTI occurs in normal urinary tracts without prior instrumentation (Reference 2).

A third strategy to classify pediatric UTIs is based on history and subsequent patient evaluation and management. Using this method, UTIs are categorized as either a first infection or a recurrent infection. The first infection is the initial UTI diagnosed by a reliable urine culture. Recurrent infections are further subcategorized as unresolved bacteriuria, bacterial persistence, or reinfection (Reference 10).

Unresolved bacteriuria is defined as persistent positive cultures with the same uropathogen isolated in the original culture. Unresolved infection is commonly the result of inadequate therapy (e.g., uropathogen resistance to selected antibiotic, patient nonadherence to prescribed antibiotic, intestinal malabsorption, subtherapeutic antibiotic urine levels). Once culture and antibiotic susceptibility results are available, unresolved bacteriuria is normally treated successfully if uropathogen resistance is identified (Reference 10).

In bacterial persistence, there is documentation of negative urine cultures after treatment of the initial UTI; however, because of incomplete eradication of the infection, the original infecting organism is isolated in subsequent episodes. Patients with documented bacterial persistence may have an underlying urinary tract abnormality (e.g., infected calculus, necrotic papillae, foreign objects), which may shield the uropathogen from antibiotic effects. It is important to identify these abnormalities, if present, given that many may be surgically treated (Reference 10).

With reinfection, there is also documentation of negative urine cultures after initial treatment, but subsequent infections are caused by organisms or strains different from the original pathogen isolated. Reinfection is usually acquired by periurethral colonization with perineal and rectal flora (i.e., retrograde ascent). Because *E. coli* is the most common infecting organism, distinguishing between reinfection and bacterial persistence can be challenging since there are several serotypes of *E. coli*. Serotyping the organism establishes reinfection if a different *E. coli* strain is isolated. However, serotyping is not commonly performed in routine clinical practice; therefore, a careful evaluation of antibiotic susceptibility patterns is helpful in distinguishing between reinfection and bacterial persistence (References 1, 4, 10). Relapse is also a term used to describe either reinfection or bacterial persistence (Reference 8).

Clinical Presentation and Diagnosis

Signs and Symptoms

Children may not present with the classic UTI signs and symptoms reported by adults (e.g., urinary frequency, dysuria, hesitancy, flank pain, turbid urine). This is particularly true in younger age groups in which nonspecific signs and symptoms are more prevalent (Reference 4, 8, 11). Neonates may present with jaundice, failure to thrive, fever, difficulty feeding, irritability, or gastrointestinal symptoms such as vomiting and diarrhea. Infants and children younger than 24 months may present

with nonspecific signs and symptoms similar to those reported in neonates with the exception of jaundice, but patients in this age group may also present with cloudy or malodorous urine, hematuria, frequency, and dysuria. Children older than 2 years are more likely to present with fever, frequency, dysuria, enuresis (in a previously toilet-trained child), hematuria, costovertebral angle pain, and/or abdominal pain. Vomiting, diarrhea, and irritability are less frequent presentations for patients older than 2 years with UTI. Urinary tract infection symptomatology in adolescent patients is typically comparable to that of adults (References 4, 8, 9).

Complications and Long-term Sequelae

Irreversible renal parenchymal damage as evidenced by renal scarring is a potential long-term complication in children having a diagnosis of pyelonephritis (i.e., upper UTI). Renal scarring may lead to end-stage renal disease (References 1, 4). Patients at risk of developing pyelonephritis include those with a diagnosis of vesicoureteral reflux (VUR), an anatomic and functional disorder whereby urine in the bladder flows retrograde into the ureter and often ascends into the kidney. If infected urine reaches the kidney, the result is acute pyelonephritis, a risk factor for renal scarring. Primary VUR (the most common type) is precipitated by a congenital defect, which results from a shortening of the submucosal ureter's longitudinal muscle; this compromises closure of the ureter with bladder filling and limits urination, thus facilitating the ascent of urine from the bladder into the ureter(s) and potentially the kidney(s). Vesicoureteral reflux is classified as grades I–V. Grades I–III are more likely to resolve spontaneously by 5 years of age than grade IV and V reflux. Probability of spontaneous resolution is lower in patients presenting at an older age and in those with bilateral reflux. More rapid resolution of VUR has been observed in African American children (References 9, 12).

Other risk factors for renal scarring include obstructive urinary tract anomalies and recurrent UTIs. The risk of renal damage is higher as the number of UTI recurrences increases. The risk of renal injury is greater for infants and young children compared with other pediatric age groups (References 1, 4, 11, 12).

Bloodstream infections associated with UTIs are more common in the younger age groups. They are reported in 18% of infants between 1 and 3 months of age, in 6% of infants between 4 and 8 months of age, and uncommonly in patients older than 1 year. Bloodstream infection may lead to meningitis, especially in patients younger than 3 months (Reference 12).

Other less common, yet serious UTI complications include pyonephrosis, renal, perirenal, and retroperitoneal abscesses; emphysematous and xanthogranulomatous pyelonephritis; and infective calculi (Reference 4).

Diagnostic Criteria

Rapid Urine Tests

Early diagnosis and appropriate treatment are essential to produce a positive outcome in the pediatric patient with UTI, particularly in infants and younger children. Because it typically takes 24 hours or more for final urine culture results to be reported by the microbiology laboratory, clinicians often employ rapid urine tests such as urine dipsticks or microscopy in evaluating a child with symptomatology suggestive of a UTI (Reference 13). Urine dipstick tests are performed at bedside, and results are available within minutes. For urine microscopy, the time it takes to receive the results varies because the sample is analyzed in the clinical laboratory; turn-around-time generally ranges between 15 minutes and 2 hours.

Dipstick analysis indirectly determines urine-specific gravity and pH as well as the presence of glucose, protein, blood, nitrites, and leukocyte esterase (LE). For the presumptive diagnosis of UTI, only nitrites and LE are associated with relatively high sensitivity (low percentage of false negatives) and high specificity (low percentage of false positives), as confirmed by bacteriuria from quantitative urine cultures. Most gram-negative urinary bacteria reduce dietary nitrates to nitrites; the positive nitrite test detects the presence of this substance and suggests a UTI. Gram-positive organisms (and some gram negatives) do not reduce nitrates to nitrites. Hence, a negative nitrite test does not rule out a UTI. Mean sensitivity for the nitrate test is 53% with a specificity of 98%. Lysed white blood cells (WBCs) release esterases. The LE test detects these substances in the urine sample and is therefore a surrogate marker for the presence of WBCs in the urine. Average sensitivity and specificity for the LE test are reported to be 83% and 78%, respectively. The combination of LE and nitrite tests increases sensitivity but not specificity (References 11, 13).

Microscopic analysis directly identifies crystals, red blood cells, WBCs (pyuria), casts, and bacteria. Of the microscopic analyses, quantification of WBCs and bacteria best correlates with a diagnosis of UTI. Pyuria is defined as 5 or more WBCs per high-power field of uncentrifuged urine sediment. Mean sensitivity for WBC microscopy is 73%, with a specificity of 81%. These values are comparable to the results reported for the less technically challenging and less costly dipstick test (i.e., LE). For bacterial microscopy, the reported mean sensitivity and specificity are 81% and 83%, respectively. Higher accuracy rates have been reported when microscopy for bacteria is performed with a Gram stain (References 8, 11, 14).

Rapid urine tests (whether dipstick or microscopic analysis) are not intended to replace urine culture as a

diagnostic tool. Rapid tests do not identify the infecting pathogen or yield antibiotic susceptibility results to guide antibiotic selection. In addition, negative rapid urine tests are reported in a significant percentage of children with a diagnosis of UTI (Reference 14).

Urine Cultures and Collection Methods

A positive urine culture is required to make the diagnosis of a UTI. The culture should be taken before antimicrobial therapy is initiated. A urine culture may be obtained by a variety of techniques. Because the distal urethra is commonly colonized with the same pathogens that cause UTIs, the number of colony-forming units (CFU) necessary to estimate infection probability depends on the method used to collect the urine sample (References 4, 12).

Suprapubic aspiration (SPA) is considered the gold standard for accurate UTI diagnosis. However, because SPA is an invasive technique, it is not routinely performed. Suprapubic aspiration involves the advancing of a 2- to 4-cm needle above the symphysis pubis through the bladder wall until urine flows into the syringe. Any number of gram-negative bacilli or greater than 10^3 gram-positive cocci is associated with a greater than 99% probability of infection (References 1, 4, 8).

Even though transurethral catheterization also represents an invasive technique, it is a commonly used method of obtaining a reliable urine sample (particularly in young children), provided the initial aliquot of the sample is discarded to reduce the potential for culturing organisms introduced into the bladder upon catheterization. For urine samples collected by transurethral catheterization, the probability of infection is 95% if 10^5 CFU of bacteria are recovered. A catheterized urine culture is considered suggestive of infection if 10^4–10^5 CFU are quantified, and repeating a culture may be warranted to establish the diagnosis (References 1, 4, 8).

In 2011, the American Academy of Pediatrics (AAP) revised its clinical practice guidelines for initial UTI in febrile children 2–24 months of age to recognize SPA and transurethral catheterization as the most reliable collection methods for diagnosing a UTI. To establish a UTI diagnosis, these guidelines recommend urinalysis results suggestive of a UTI (i.e., pyuria and/or bacteriuria) plus the presence of 50,000 CFU/mL or more of uropathogen collected by SPA or catheterization (Reference 11).

Clean void urine samples are simple to perform and are noninvasive. A clean void urine sample is obtained using the clean-catch midstream technique and is commonly used in older children and adolescents. After appropriate topical disinfection of the genitalia, the patient urinates the first aliquot of the sample into the toilet, after which the collection cup is placed under the urine stream to collect the laboratory sample. Periurethral and preputial organisms contaminate clean-catch specimens in a significant percentage of samples, making interpretation of positive results challenging. In females, 10^5 CFU or greater of bacteria confers a high probability of infection (i.e., 80% to 95%, depending on whether one, two, or three positive urine specimens were recovered). In males, greater than 10^4 CFU of bacteria makes infection likely (References 1, 4, 8).

A bagged specimen is an alternative method of urine collection that involves attaching a plastic bag to the perineum to collect the urine specimen; the bagged urine technique may be used to collect a sample from infants and smaller children. Bagged urine samples are associated with high rates of false-positive results and are generally not reliable to establish the diagnosis of a UTI. However, a negative result on a bagged urine sample is helpful in ruling out a UTI (References 8, 11).

Imaging Studies

Urinary tract infections in infants and young children may serve as an indicator of urinary tract abnormalities; therefore, imaging studies have traditionally been recommended after a first UTI to identify potential urinary tract anomalies that may predispose the young child to renal disease. Imaging studies performed in pediatric patients include renal and bladder ultrasonography (US), intravenous pyelography, voiding cystourethrography (VCUG), radionuclide cystography, renal cortical scan, computed tomography, and/or magnetic resonance imaging (MRI) (References 6, 8, 11).

Ultrasonography offers a noninvasive method to evaluate anatomy (e.g., renal size and various aspects of the parenchyma); it may also reveal obstructive lesions. Ultrasonography identifies hydronephrosis, dilation of distal ureters, bladder wall hypertrophy, and presence of ureteroceles. Intravenous pyelography, which requires parenteral administration of iodinated contrast dye, was previously used to detect such anomalies; however, US is currently preferred to intravenous pyelography for anatomic evaluation of the urinary tract because it effectively reveals these abnormalities but is safer, less invasive, and more cost-effective. Ultrasonography does not reliably detect VUR (References 6, 8, 11).

Voiding cystourethrography or radionuclide cystography is effective in diagnosing and grading VUR. Both of these imaging studies involve radiation exposure and catheterization. Radionuclide cystography, however, does not reveal male urethral or bladder abnormalities, whereas VCUG does (Reference 5).

Renal cortical scans, also known as scintigraphy, require injection of the radioisotope DMSA (^{99m}technetium dimercaptosuccinic acid) or ^{99m}technetium glucoheptonate. It is a sensitive test for assessing renal

scarring or identifying acute changes associated with pyelonephritis. Renal cortical scans are also useful in diagnosing mass lesions such as neoplasms and abscesses (References 8, 11).

Computed tomography and MRI studies best visualize renal abscesses. Computed tomography is more commonly used because it is readily available. Magnetic resonance imaging may yield better soft tissue resolution and diagnostic sensitivity (Reference 8). There is some evidence to support the use of MRI for the evaluation of renal scarring (References 15, 16).

Guidelines for follow-up imaging studies vary. A published algorithm for imaging decisions in children with UTI recommends US plus VCUG for girls 36 months or younger, girls between 3 and 7 years of age with a temperature of 101.3°F (38.5°C) or higher, and for all boys regardless of age. The algorithm recommends observation without imaging for girls 3–7 years of age with a temperature less than 101.3°F (38.5°C) and girls older than 7 (Reference 5). Alternatively, the 2011 AAP clinical practice guideline for febrile infants and children 2–24 months of age recommends US after the initial UTI but not VCUG routinely, reserving the latter for a recurrent episode of febrile UTI (Reference 11). More conservative use of US has been proposed. Some authors advocate reviewing the US from the third trimester of pregnancy (if available) after the first uncomplicated febrile UTI in children younger than 3 years. If the US is unavailable or considered unreliable, it should be performed on the child. Children with atypical UTI presentations also benefit from ultrasonography (Reference 17).

Other Laboratory Tests

Depending on the clinical presentation, a complete blood cell count, C-reactive protein, and blood culture may provide valuable data when treating an acutely ill child. A basic metabolic panel may expose electrolyte abnormalities if the child is dehydrated or renally compromised (References 4, 12, 18).

Treatment

Antibiotic therapy is initiated empirically on the basis of local (or regional) susceptibility patterns of the selected antibiotic against the targeted organism(s). After reviewing the patient's allergy history, newer-generation cephalosporins, trimethoprim/sulfamethoxazole, or β-lactam/β-lactamase inhibitor combination are commonly selected for empiric UTI treatment. Once culture and susceptibility results are available, antibiotic therapy is adjusted accordingly. Patients with a history of anatomic or functional urinary tract abnormalities, recurrent UTIs, uncommon pathogens, catheter use, or immunodeficiency states may require more individualized antibiotic coverage (References 11, 12).

Parenteral Antibiotics

Children, particularly those younger than 2 years, may require administration of parenteral antibiotic therapy. Criteria for parenteral antibiotic administration include acutely ill ("toxic") children, infants younger than 2 months, immunocompromised patients, children who are unable to retain oral intake or who are dehydrated, and cases in which adherence to, obtaining, and/or administering oral antibiotics is uncertain (References 1, 11, 17).

Table 2 lists the most commonly used parenteral antibiotics prescribed for the treatment of pediatric UTIs, together with pediatric dosing recommendations and common and/or severe adverse drug events reported. The cephalosporins, aminoglycosides, and fluoroquinolone listed in Table 2 are generally active against uropathogens in the *Enterobacteriaceae* family (e.g., *E. coli, Klebsiella* spp., *Citrobacter* spp., *Enterobacter* spp., *M. morganii, P. mirabilis, P. stuartii,* and *Serratia* spp.). The newer-generation cephalosporins are more β-lactamase stable than the earlier generations and thus are more active against β-lactamase–producing pathogens and suitable for empiric therapy. Cefotaxime and ceftriaxone have comparable antimicrobial spectra of activity and may be used interchangeably in most instances; however, ceftriaxone is not routinely recommended for neonates. The drug is highly protein bound (more than 90% bound to albumin), and in hyperbilirubinemic neonates, bilirubin displacement from its albumin binding sites increases the risk of kernicterus. In addition, ceftriaxone is contraindicated in neonates receiving (or who may require) calcium-containing intravenous solutions; crystalline material has been recovered at autopsy from the lungs and kidneys of a limited number of neonates administered this combination. If an anti-pseudomonal antibiotic is indicated, aminoglycosides, ciprofloxacin, ceftazidime, and cefepime are active against *P. aeruginosa*, an organism recovered in 13.1% of nosocomial UTIs (Reference 4). Most gram-negative uropathogens produce β-lactamases; consequently, a significant percentage of these organisms are resistant to ampicillin. Ampicillin monotherapy is not a preferred empiric antibiotic selection for UTI. Ampicillin may be used empirically in combination with an aminoglycoside or a latter-generation cephalosporin. Unlike cephalosporins, ampicillin is microbiologically active against enterococci, particularly *Enterococcus faecalis* (References 1, 11, 19).

Duration of parenteral therapy depends on the patient's clinical response to therapy. Parenteral antibiotics are continued until the patient is afebrile and clinically stable, after which the antibiotic is switched to an appropriate oral agent (Reference 1). A study of infants younger than 6 months reported no difference in

readmission rate at 30 days after discharge for patients administered antibiotics intravenously for 3 days or less versus 4 days or more, provided the infants completed a 10- to 14-day total antibiotic course (Reference 20).

Oral Antibiotics

An oral antibiotic is typically prescribed to pediatric patients with UTIs for one of the following indications: (1) to complete a UTI treatment course in a patient initiated on parenteral antibiotics or (2) as initial treatment of the UTI in a child presenting to an emergency department or physician's office who does not meet criteria for parenteral antibiotics. Advantages of oral antibiotic therapy include ease of administration and overall lower cost. Studies of children 1 month and older treated for pyelonephritis showed similar efficacy between oral and intravenous/oral sequential therapy. There was no statistical difference in renal scarring between oral and intravenous/oral treatment groups. The oral antibiotics used in these trials were amoxicillin/clavulanate, cefixime, and ceftibuten (References 21–23).

Table 3 identifies common oral antibiotics used for the empiric treatment of pediatric UTIs; the table includes the pediatric dosing recommendations and select adverse drug events reported. Documented safety and efficacy are the primary considerations when selecting an oral antibiotic for the treatment of UTIs. If a liquid formulation is indicated, an important consideration is palatability because that influences patient adherence to the prescribed regimen. Studies evaluating the taste of pediatric antibiotic oral formulations report substantial variability in palatability for the products tested. One study rates the palatability of some of the antibiotic suspensions included in Table 3. The rankings in decreasing order of palatability are as follows: cefixime, ceftibuten, trimethoprim/sulfamethoxazole, amoxicillin/clavulanate, and cefpodoxime (Reference 24). Cost and formulary status are additional considerations when selecting an oral antibiotic (Reference 24). Another factor to consider when selecting an antibiotic empirically is the *E. coli* local resistance pattern. Avoid selecting an antibiotic for empiric use if the local

Table 2. Parenteral Antibiotics Commonly Used for Pediatric UTIs (References 1, 11, 19)

Antibiotic	Pediatric Dosage[a,b]	Adverse Drug Events
Ampicillin	100–200 mg/kg/day divided every 4–6 hours	Hypersensitivity, hematologic toxicity, N/V/D, increased LFTs, interstitial nephritis
Cefazolin (Ancef, Kefzol)	50 mg/kg/day divided every 6–8 hours	Hypersensitivity, hematologic toxicity, N/V/D, increased LFTs, increased serum creatinine
Cefotaxime (Claforan)	100–150 mg/kg/day divided every 6–8 hours	Similar to cefazolin
Ceftriaxone (Rocephin)	50–75 mg/kg/day divided every 12–24 hours	Similar to cefazolin plus biliary sludging, cholelithiasis
Ceftazidime (Fortaz)	100–150 mg/kg/day divided every 8 hours	Similar to cefazolin
Cefepime (Maxipime)	100 mg/kg/day divided every 12 hours	Similar to cefazolin
Ciprofloxacin[c] (Cipro)	18–30 mg/kg/day divided every 8 hours	Tendon rupture, Achilles tendonitis, N/V/D, increased LFTs, increased serum creatinine
Gentamicin (Garamycin)	5–7.5 mg/kg/day divided every 8–24 hours	Nephrotoxicity, ototoxicity, neuromuscular blockade
Tobramycin (Nebcin)	5–7.5 mg/kg/day divided every 8–24 hours	Similar to gentamicin

[a]Doses referenced assume normal renal function and are consistent with dosing recommendations for children outside the neonatal period. For neonatal dosing recommendations, consult appropriate reference.
[b]Doses for larger children and adolescents are typically capped to the adult dose when weight-based dosing results in a higher value than the standard adult dose for the indication.
[c]Ciprofloxacin is approved by the U.S. Food and Drug Administration (FDA) for complicated UTIs and pyelonephritis in children 1–17 years of age.
D = diarrhea; LFT = liver function test; N = nausea; UTI = urinary tract infection; V = vomiting.

resistance rate against the targeted organism is 20% or higher (References 12, 25). Once the organism is identified in culture, deescalating to narrower-spectrum agents should be considered on the basis of susceptibility results and the patient's clinical condition.

Drug-specific properties are another important consideration. Use of trimethoprim/sulfamethoxazole should be avoided in children younger than 2 months because sulfonamides are highly protein bound and, in hyperbilirubinemic patients, may displace bilirubin and potentially cause kernicterus. Nitrofurantoin should be avoided in patients with glucose-6-dehydrogenase deficiency (G-6-PD) because of the risk of precipitating hemolytic anemia. Nitrofurantoin is contraindicated if creatinine clearance is less than 60 mL/minute because therapeutic urine concentrations are not attained in renal insufficiency (Reference 19). Nitrofurantoin should also be avoided in the treatment of febrile infants with UTIs; parenchymal and serum concentrations attained may be insufficient to treat pyelonephritis or urosepsis (Reference 11).

The AAP recommends a 7- to 14-day treatment course for children between 2 months and 2 years of age (Reference 11). Antibiotic courses of 10–14 days are commonly prescribed for children and adolescents with a diagnosis of pyelonephritis; courses of 3–7 days are generally used for the treatment of cystitis (Reference 9). For uncomplicated lower UTIs, even shorter treatment courses (2–4 days) with oral antibiotics have been reported as effective (References 26, 27).

UTI Prophylaxis

The rationale for antibiotic prophylaxis after active UTI treatment is maintaining sterilization of the urine. The goal is to prevent irreversible renal parenchymal damage (renal scarring) and its sequelae. The antibiotic selected for prophylaxis is administered at a reduced dose, achieving therapeutic urine concentrations while delivering low antibiotic levels to the bowel to minimize its effect on normal intestinal flora. Traditionally, the following subgroups have been considered for antibiotic prophylaxis: neonates or infants being evaluated for anatomic

Table 3. Oral Antibiotics Commonly Used for Empiric Treatment of Pediatric UTIs (References 1, 19, 21–23)

Antibiotic	Pediatric Dosage[a,b]	Adverse Drug Events
Amoxicillin/clavulanate (Augmentin)	40–50 mg/kg/day divided every 8–12 hours	N/V/D, abdominal pain, hypersensitivity
Cefixime (Suprax)	8 mg/kg/dose every 12 hours × 1 day; then 8 mg/kg once daily	N/V/D, abdominal pain, hypersensitivity
Cefpodoxime (Vantin)	10 mg/kg/day divided every 12 hours	Similar to cefixime
Ceftibuten (Cedax)	9 mg/kg/dose every 12 hours × 1 day; then 9 mg/kg once daily	Similar to cefixime plus serum sickness–like reaction
Cephalexin (Keflex)	50 mg/kg/day divided every 6 hours	Similar to cefixime
Ciprofloxacin[c] (Cipro)	20–40 mg/kg/day divided every 12 hours	N/V/D, dizziness, photosensitivity, tendon rupture, Achilles tendonitis
Nitrofurantoin[d] (Furadantin, Macrodantin)	5–7 mg/kg/day divided every 6 hours	N/V, anorexia, hypersensitivity, hematologic toxicity, urine discoloration
Trimethoprim/sulfamethoxazole (Bactrim, Septra)	8–12 mg/kg/day trimethoprim divided every 12 hours	Hypersensitivity, N/V/D, hematologic toxicity, interstitial nephritis

[a]Doses referenced assume normal renal function and are consistent with dosing recommendations for children outside the neonatal period. For neonatal dosing recommendations, consult appropriate reference.
[b]Doses for larger children and adolescents are typically capped to the adult dose when weight-based dosing results in a higher value than the standard adult dose for the indication.
[c]Ciprofloxacin is approved by the U.S. Food and Drug Administration (FDA) for complicated UTIs and pyelonephritis in children 1–17 years of age.
[d]Nitrofurantoin should only be used for cystitis in patients with a creatinine clearance of 60 mL/min or greater.
D = diarrhea; N = nausea; UTI = urinary tract infection; V = vomiting.

Table 4. Oral Antibiotics Commonly Used for UTI Prophylaxis in Children (References 8, 19)

Antibiotic	Pediatric Dosage[a,b]	Adverse Drug Events
Amoxicillin (Amoxil)	10–15 mg/kg once daily at bedtime	N/V/D, abdominal pain, hypersensitivity
Cephalexin (Keflex)	12–15 mg/kg once daily at bedtime	N/V/D, abdominal pain, hypersensitivity
Nitrofurantoin (Furadantin, Macrodantin)	1–2 mg/kg once daily at bedtime	N/V, anorexia, flatulence, headache, hypersensitivity, urine discoloration
Trimethoprim/sulfamethoxazole (Bactrim, Septra)	Trimethoprim 2 mg/kg at bedtime OR Trimethoprim 5 mg/kg twice weekly at bedtime	Hypersensitivity, N/V/D, hematologic toxicity, interstitial nephritis

[a]Doses referenced assume normal renal function and are consistent with dosing recommendations for children outside the neonatal period. For neonatal dosing recommendations, consult appropriate reference.
[b]Doses for larger children and adolescents are typically capped to the adult dose when weight-based dosing results in a higher value than the standard adult dose for the indication.
D = diarrhea; N = nausea; UTI = urinary tract infection; V = vomiting.

or functional urinary tract abnormalities; children with a history of VUR, dysfunctional voiding, or partial urinary obstruction; immunosuppressed patients; and children with recurrent UTIs despite normal urinary anatomy and function. In general, prophylactic antibiotics are continued until resolution of the underlying condition(s) predisposing the patient to UTIs (References 1, 6).

The antibiotics listed in Table 4 are commonly used for UTI prophylaxis in children. Typically, they yield comparable outcomes, provided the selected antimicrobial agent is active against the targeted organisms (References 1, 8). In patients with recurrent infections, careful evaluation of previous culture and susceptibility results serves as a valuable guide in antibiotic selection. The use of prophylactic cephalosporins for patients with VUR may result in untoward consequences. In a study of breakthrough UTIs in pediatric patients with VUR, there was a greater likelihood of culturing extended-spectrum β-lactamase–producing organisms or non–*E. coli* multidrug-resistant uropathogens in the cephalosporin prophylaxis groups than in the trimethoprim/sulfamethoxazole arm of the study (Reference 28).

The routine use of UTI prophylaxis is the subject of considerable debate. The 2011 AAP clinical practice guidelines do not recommend prophylactic antibiotics to prevent UTI recurrences. After the initial UTI, the clinician instructs the parents or guardians to seek prompt medical attention (i.e., within 48 hours) for any future febrile illness because early treatment is preferred to limit potential renal damage (Reference 11). A Cochrane review of the pediatric literature concludes that prophylactic antibiotics reduce the risk of recurrent symptomatic UTIs; however, their benefit is limited, and the increased risk of bacterial resistance needs to be considered (Reference 29). Another meta-analysis recommends against the routine use of antibiotic prophylaxis in children at risk of developing UTIs, citing lack of evidence supporting a positive benefit (Reference 30). One study reports an increased risk of resistant infections but no decrease in risk of recurrent UTIs associated with antibiotic prophylaxis (Reference 31).

Initiation of prophylaxis should be considered if the benefits are expected to outweigh the risks after a thorough evaluation of the patient's clinical condition and risk factors for adverse UTI sequelae. Family involvement is imperative in the decision of whether to initiate prophylactic antibiotics.

Conclusions

Urinary tract infections are a common disease state in children. Children with UTIs are at increased risk of long-term morbidity, including irreversible renal damage and its sequelae. Signs and symptoms in the young child may be nonspecific, making diagnosis more challenging on presentation. Specific rapid urine tests are useful in the initial patient workup to support a presumptive diagnosis pending culture results. A positive urine culture is required to make the diagnosis of UTI. The predominant pathogen isolated is *E. coli*. Follow-up imaging studies may be necessary to identify anatomic or functional abnormalities, particularly in the young infant or child with recurrent UTIs. Prompt and effective antimicrobial treatment is indicated in acute infection to reduce the risk of subsequent complications.

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CHAPTER 40

Bone and Joint Infections

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Learning Objectives

1. Distinguish between the clinical presentation of osteomyelitis and infectious arthritis.
2. List the common etiologic organisms associated with osteomyelitis and infectious arthritis.
3. List appropriate antibiotic treatments for osteomyelitis and infectious arthritis.
4. Discuss monitoring parameters in patients with osteomyelitis and infectious arthritis.

Abbreviations in This Chapter

CA-MRSA	Community-associated methicillin-resistant *Staphylococcus aureus*
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
MRSA	Methicillin-resistant *Staphylococcus aureus*
PVL	Panton-Valentine leukocidin
WBC	White blood cell count

Introduction

Bone and joint infections are classified as osteomyelitis or infectious arthritis. These infections are usually associated with long treatment courses of antimicrobial agents and can lead to significant morbidity in some cases (Reference 1). Bone and joint infections can affect patients of all ages, including children. The following sections will discuss osteomyelitis and infectious arthritis in detail.

Osteomyelitis

Definition

Osteomyelitis is defined as inflammation of the bone and/or bone marrow, usually accompanied by a microbial infection (References 2, 3). Although infection can occur with any bone throughout the body, the long bones are often affected in infants and children. Infections can be caused by bacteria, fungi, and mycobacteria. The infection is typically acute in origin, but all bone infections can progress to chronic osteomyelitis with a risk of necrosis of the bone.

Epidemiology and Classification

The incidence of osteomyelitis has been reported as around 1 in 5000 children (Reference 4). It accounts for about 1% of all pediatric hospitalizations. One-half of the occurrences are in children younger than 5 years. Males are more commonly affected than females, with a ratio of about 2:1, respectively. Most infections involve one site, but up to 20% of children can present with multifocal osteomyelitis (References 1, 5). Neonatal osteomyelitis occurs in around 1–3 infants per 1000 neonatal intensive care admissions and is associated with a higher incidence of multifocal osteomyelitis compared with older children (Reference 6).

The overall incidence of osteomyelitis has been decreasing during the past several decades (Reference 7). However, there are an increasing number of osteomyelitis cases because of resistant gram-positive organisms. In addition, more virulent strains of bacteria have emerged as causative organisms. In particular, Panton-Valentine leukocidin (PVL)-positive community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) strains are of concern. Evidence has shown infections caused by these strains are associated with more severe disease and increased complications.

Historically, osteomyelitis has been classified by symptom onset and duration. Patients were identified as having acute, subacute, or chronic osteomyelitis. Acute infections occur within 1–2 weeks of disease onset, subacute infections last for a few weeks but less than 1 month, and chronic infections last more than 1 month with the presence of bone necrosis (References 8, 9). Acute osteomyelitis accounts for 50% of infections and is more common in children (References 1, 8). Subacute and chronic osteomyelitis typically occur in adult patients.

Waldvogel Classification

In 1970, Waldvogel developed a classification system using both the pathogenesis and duration of the infection (References 10–12). The Waldvogel system classifies osteomyelitis as hematogenous, contiguous, or chronic. Hematogenous osteomyelitis is spread through the bloodstream and is commonly seen in neonates, infants, and children. Contiguous osteomyelitis is spread through an adjacent soft tissue infection or by direct inoculation into the bone (e.g., trauma, puncture wounds, and surgery). Most contiguous infections in pediatric patients are associated with puncture wounds of the foot or patella

(Reference 8). Osteomyelitis of the foot after a puncture wound occurs in about 1.5% of cases (Reference 13). Chronic osteomyelitis develops when the bone becomes necrotic because of the loss of blood supply. The disadvantage of the Waldvogel classification system is that it was not designed to guide surgical or antimicrobial therapy.

Cierny-Mader Staging System

Cierny-Mader staging is another classification system for osteomyelitis that is based on anatomic location and physiologic status of the patient (Reference 14). Initially established for adults, it can also be used to stage osteomyelitis in children. The staging, developed to allow guidance for treatment and/or surgical management, is particularly useful for infections involving long bones. There are four stages that describe the anatomic location and three host classifications (A, B, or C). Stage 1 (medullary) is an infection entirely within the bone marrow from hematogenous spread. Stage 2 (superficial) involves the surface of the bone, usually from a contiguous focus or direct inoculation. Stage 3 (localized) involves both the surface of the bone and the bone marrow. Stage 4 (diffuse) involves the entire thickness of the bone. The physiologic status is defined by the host's ability to mount an immune response (i.e., immunocompetent vs. immunocompromised). Patients are classified into the following categories: healthy (C), presence of local host compromise (BL), presence of systemic host compromise (BS), presence of both local and systemic compromise (BLS), and presence of severe compromise that results in the treatment being worse than the disease (C). Systemic host factors include malnutrition, renal or hepatic failure, diabetes, and immunosuppression. The most common local host factors are venous stasis, major vessel compromise, arteritis, scarring, and neuropathy.

Pathophysiology

Microorganisms can enter the bone through the bloodstream secondary to bacteremia, by direct inoculation (e.g., trauma, surgery), or from an adjacent soft tissue infection. Hematogenous spread to the bone occurs most commonly in pediatric patients because of the rich vascular supply and slow blood flow that is present in the metaphysis, particularly of long bones. The infecting organism initially affects the capillary loop near the epiphyseal growth plate to form a microabscess and localized inflammation. The organism then continues to travel through large venous sinusoids to areas of slow blood flow, where there is continued recruitment of inflammatory mediators, phagocytic cells, and toxins. Prostaglandins are produced in response to bone destruction and can decrease the amount of bacteria needed to cause infection (Reference 2). Reactive bone formation occurs around the area of infection. The infection leads to edema and increased vascular permeability, which allows elevation of the periosteum. Eventually, the bacteria can enter the subperiosteal space and continue to form abscesses that become isolated from the blood supply within the bone. Once the blood supply is diminished, dead bone, or sequestra, are formed. *S. aureus* is of concern because it can express bacterial adhesion proteins, which promote attachment to the bone matrix (collagen, fibronectin, laminin) and cartilage (Reference 15). In addition, *S. aureus* strains produce endotoxins capable of suppressing the local inflammatory response. If the infection spreads into the adjacent growth plate and epiphysis, joint damage and concomitant infectious arthritis can occur.

The most common cause of osteomyelitis in children is acute hematogenous osteomyelitis. Although the metaphysis of the long bones is most commonly affected, the bones of the hip, knee, and shoulder can also be involved, especially with a concomitant joint infection (Reference 16). Osteomyelitis of the lower extremities has been reported in up to 72% of patients (Reference 17). In neonatal osteomyelitis, there is a higher frequency of concomitant septic arthritis (up to 75% of cases), particularly in the hip, shoulder, and knee (Reference 13). In children older than 1 month, adjacent infectious arthritis of the joint has been reported in up to 40% of patients (Reference 18). Adjacent infectious arthritis of the joint is most common in patients younger than 18 months.

Microorganisms

There is usually only one infecting organism involved in acute hematogenous osteomyelitis. The most common organism is *S. aureus*, which accounts for about 80% of cases. The percentage of infections caused by methicillin-resistant *S. aureus* (MRSA) strains varies greatly by region, but it may approach 50% in some areas (Reference 1). Group A *Streptococcus* (*Streptococcus pyogenes*), *Streptococcus pneumoniae*, and *Kingella kingae* are also common causes in infants and children (References 19-21). *S. aureus*, *S. pyogenes*, and *S. pneumoniae* are gram-positive organisms found on the skin and in the oropharynx. *K. kingae* is a fastidious gram-negative coccobacillus that is part of the normal respiratory flora. *Haemophilus influenzae* type b (Hib) is becoming rare because of universal childhood immunization against this pathogen. After 4 years of age, the incidence of *H. influenzae* is dramatically decreased (Reference 22). Table 1 and Table 2 list the most common organisms seen in osteomyelitis by patient age and clinical condition.

Other organisms that cause osteomyelitis infrequently include *Mycobacterium* spp., *Bartonella henselae*, *Borrelia burgdorferi*, fungi (e.g., *Histoplasma*, *Cryptococcus*, *Blastomyces*, *Actinomyces*, *Coxiella*), *Pasteurella multocida*,

and anaerobic bacteria (e.g., *Bacteroides*, *Clostridium*, *Fusobacterium*, *Peptostreptococcus*) (References 25, 26). In particular, *Mycobacterium, Bartonella*, and fungi are usually found in immunocompromised patients.

Contiguous osteomyelitis in children most often occurs after direct inoculation of bacteria from a traumatic wound. Anaerobic bacteria should be considered additional causative organisms in these cases. It is uncommon for children to develop osteomyelitis secondary to a contiguous infection. However, these cases usually involve a primary infection in the oromaxillary cavity (e.g., sinus, tooth, mastoid bone) (Reference 1).

The most common cause of chronic osteomyelitis in children is inadequate treatment of a hematogenous bone infection (Reference 26). The presence of an orthopedic implant can also be associated with the development of chronic osteomyelitis.

Table 1. Common Pathogens in Pediatric Osteomyelitis Based on Patient Age

Age	Organism
Neonate (< 1 month)	*Staphylococcus aureus* Group B streptococci (*Streptococcus agalactiae*) Gram-negative enteric organisms (*Escherichia coli, Klebsiella oxytoca*) Candida spp.
1 month to 5 years	*Staphylococcus aureus* *Streptococcus pyogenes* *Streptococcus pneumoniae* *Kingella kingae*
> 5 years	*Staphylococcus aureus* *Streptococcus pyogenes*

Table 2. Common Pathogens in Pediatric Osteomyelitis Based on Comorbid Conditions

Organism	Clinical Condition
Salmonella[a]	Sickle cell disease
Staphylococcus epidermidis	Foreign body
Pseudomonas aeruginosa[b]	Puncture wounds to the feet Immunocompromised
Bartonella henselae	Human immunodeficiency virus Kitten exposure
Fungi	Immunocompromised
Anaerobic bacteria	Dental abscess
Pasteurella multocida	Human or animal bite

[a]Reference 23.
[b]Reference 24.

Risk Factors

Risk factors for the development of hematogenous osteomyelitis include bacteremia, nonpenetrating trauma, and long-term, indwelling intravenous catheters. Pediatric patients are at increased risk of acute hematogenous osteomyelitis because the metaphyseal plate has a rich blood supply, and infectious spread from bacteremia is more likely. Additional risk factors specific for neonates include placement of an umbilical catheter and frequent heel stick blood draws. Risk factors for developing contiguous osteomyelitis include penetrating trauma, animal bites, puncture wounds, and adjacent soft tissue infections.

Clinical Presentation and Diagnosis

Signs and Symptoms

The clinical presentation usually involves local inflammation, pain and swelling, and systemic symptoms such as fever, irritability, and lethargy. Clinical presentation also depends on the origin of the infection and can vary with age. Pseudoparalysis is the cardinal sign in neonates and young children, although irritability is the most common symptom in this age group (Reference 27). Pseudoparalysis occurs when the infant appears unable to move the affected arm or leg but has no true paralysis. In older children, the pain is usually more localized, and a common presentation is refusal to bear weight or presence of a limp. Fever is usually absent in most children with a diagnosis of osteomyelitis. Infections caused by *K. kingae* are usually preceded by an upper respiratory tract infection.

Clinically, patients with a PVL-positive strain of CA-MRSA present differently from those without the presence of PVL. Typical clinical manifestations associated with a PVL-positive strain include multiple infection sites, myositis, subperiosteal abscess, and severe life-threatening co-infections (Reference 28). In addition, chronic osteomyelitis is more likely to be diagnosed on admission or to develop in patients with PVL-positive isolates compared with patients having PVL-negative strains (Reference 29).

Diagnostic Criteria

Diagnosis of osteomyelitis is based on clinical presentation, presence of certain laboratory markers, and imaging studies to detect infection in the bone. Laboratory data indicative of osteomyelitis include an elevated white blood cell count (WBC); increased inflammatory markers, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); presence of bacteria from a blood culture or biopsy of the bone of adjacent infected soft tissue; and abnormal physical examination, such as pain or tenderness. Blood cultures are only positive in about 50% of cases; thus, the presence of a negative

blood culture cannot rule out osteomyelitis (Reference 30). Polymerase chain reaction analyses have been useful in detecting *K. kingae* because it is difficult to culture using standard laboratory methods (Reference 31).

The CRP, a nonspecific, acute inflammatory marker, is useful early in the disease process. It typically peaks a few days after an acute infection and normalizes once treatment has begun. The ESR is a marker of chronic inflammation and can be used to guide long-term treatment and disease management. The CRP has been shown to predict recovery better than WBC or ESR (Reference 32). A normal WBC and CRP do not exclude a diagnosis of osteomyelitis. Patients with osteomyelitis caused by PVL-producing *S. aureus* have been found to have a higher mean ESR, CRP, and absolute neutrophil count compared with patients who do not have a PVL-producing strain (Reference 33).

If a biopsy of the infected bone is performed, histopathologic and microbiologic examinations of the bone are helpful diagnostic tools. The procedure is usually performed with guided computed tomography (CT) or ultrasonography. The presence of bacteria from a bone biopsy is diagnostic for osteomyelitis.

Imaging Procedures

Imaging studies are helpful in diagnosing osteomyelitis. Common studies include standard radiography, radionuclide imaging or scintigraphy, magnetic resonance imaging (MRI), CT scan, and positron emission tomography. Standard radiographs can detect soft tissue swelling but are usually normal during the first 2–3 weeks of the infection (see Figure 1). Standard radiographs are useful in detecting fractures or malignancies and thus in ruling out osteomyelitis. Radionuclide imaging (i.e., bone scan) is performed with an intravenous radiopharmaceutical (e.g., technetium-99m) administration. Radiography will show increased uptake of the technetium-99m in areas with inflammation. The sensitivity of radionuclide imaging is between 80% and 100%, but the specificity is low because it cannot distinguish infection from trauma or malignancy (Reference 1). This test is most useful when the exact infection site cannot be determined or when multifocal sites are suspected.

Magnetic resonance imaging has the best results for imaging, with 97% sensitivity and 92% specificity (References 34, 35). In fact, MRI is preferred to scintigraphy because of its ability to detect extraosseous complications such as subperiosteal abscesses, septic arthritis, and deep venous thrombosis (see Figure 2) (Reference 36). Disadvantages of MRI compared with scintigraphy include high cost, inability to distinguish postsurgical inflammation from osteomyelitis, and patient sedation requirement. Computed tomography scans can also be performed to visualize bony structures, but they are less specific than MRI studies. Positron emission tomography is an imaging study that uses a nonspecific tracer that accumulates at infection or inflammation sites. In the management of osteomyelitis, it has been shown useful in diagnosing chronic osteomyelitis and as a follow-up study to assess response to therapy (Reference 37).



Figure 1. Radiographic image depicting long-bone regions (left labels) and bony changes (right labels) caused by *Staphylococcus aureus* osteomyelitis occurring in the distal right humerus of a 12-month-old infant (Reference 16).

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Course and Prognosis

Acute hematogenous osteomyelitis is associated with a favorable prognosis once bacteremia has cleared. Recurrence is reported in up to 5% of cases overall and in up to 50% of neonatal cases (Reference 1). Relapse has been reported in 30% to 60% of children who did not have abscess drainage, if present, despite adequate antimicrobial therapy (Reference 38). In one study, monitoring serial CRP values was helpful in identifying patients who might have a complicated course as well as in predicting outcomes (Reference 39). If CRP

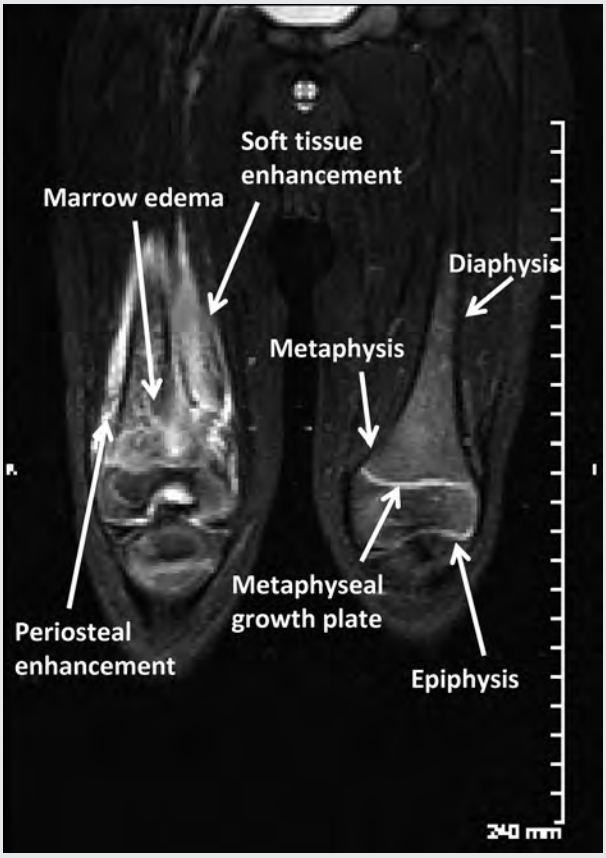


Figure 2. Magnetic resonance image depicting long-bone regions (left femur) and extensive marrow edema and significant enhancement of the periosteum and adjacent soft tissues (right femur) caused by *Staphylococcus aureus* osteomyelitis occurring in the distal right femur of a 26-month-old infant (Reference 16).

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values remained high on day 3 of treatment, the patient was more likely to have a complicated clinical course (determined at a follow-up visit 1–2 months after discharge). However, if CRP values fell to normal levels by day 5, patients were more likely to be asymptomatic at follow-up.

Complications of osteomyelitis include persistent bacteremia, subperiosteal abscesses, venous thromboembolism, and progression to chronic osteomyelitis (Reference 35). Furthermore, permanent abnormalities of bone growth are possible. Chronic osteomyelitis, which may persist for several months, is usually managed with a combination of prolonged courses of antimicrobial therapy and surgical management. The prognosis of contiguous osteomyelitis depends on early diagnosis and aggressive therapy to avoid progression to chronic osteomyelitis.

Treatment

Goals of Therapy

The goals of antimicrobial therapy are eradication of the organism, resolution of infection, and prevention of long-term sequelae. Because clinical practice guidelines for the management of osteomyelitis do not presently exist, the infection is best managed with a multidisciplinary team of clinicians. Recommendations for the diagnosis and treatment of pediatric osteomyelitis are based on expert opinion, case series, and small clinical trials. Early initiation of appropriate empiric antimicrobial therapy is crucial to prevent complications from osteomyelitis. Table 3 and Table 4 list treatment options and dosing information for specific organisms associated with osteomyelitis. Important considerations when selecting an antibiotic for presumed osteomyelitis include infection type, etiologic organisms, availability of culture and sensitivity results, host factors, and antibiotic characteristics. The key antibiotic characteristics to consider include local resistance patterns, penetration into the bone, and potential for systemic toxicities.

Pharmacologic Therapy

Specific considerations are necessary for both empiric and bacteria-specific treatment. Currently, there is no consensus on the appropriate duration of intravenous therapy or total duration of therapy for osteomyelitis. Clinicians must select treatment duration on the basis of clinical presentation, risk factors, infection site, and patient age. Therapy duration for acute osteomyelitis is typically 4–6 weeks. Chronic osteomyelitis requires treatment with both surgical and medical intervention. Patients may require antimicrobial therapy for up to 6–12 months.

Initial therapy typically includes intravenous antibiotics, which may be used for up to 2 weeks before switching to oral therapy. Recent evidence has shown that an earlier transition from intravenous to oral therapy results in clinical outcomes and treatment failures similar to those in prolonged intravenous therapy (References 41-43). A systematic review of 12 studies found that patients receiving 7 days of intravenous therapy followed by oral therapy had similar cure rates at 6 months compared with patients receiving greater than 1 week of intravenous therapy (95.0% vs. 98.8%) (Reference 41). A study of 29 pediatric patients who were treated for acute osteomyelitis with a median of 4 days of intravenous therapy followed by 28 days of oral therapy showed no complications or treatment failures at the 6-month follow-up (Reference 42). Another study of 131 pediatric patients with culture-positive acute hematogenous osteomyelitis showed a favorable outcome in patients who received 2–4 days of intravenous therapy followed by oral therapy for 20–30 days (Reference 43). Furthermore, patients with prolonged

Table 3. Directed Antibiotic Therapy for the Management of Bone and Joint Infections

Microorganism	Preferred Therapy	Alternative Therapies
Staphylococcus aureus Methicillin-susceptible (MSSA)	Nafcillin or oxacillin	Cefazolin Oral alternatives: dicloxacillin or cephalexin
Staphylococcus aureus Methicillin-resistant (MRSA)	Vancomycin	Linezolid or daptomycin
Community-associated MRSA	Vancomycin or clindamycin	Linezolid or daptomycin
Streptococcus agalactiae	Penicillin G or ampicillin	Cefotaxime or ceftriaxone
Staphylococcus epidermidis	Vancomycin	Daptomycin
Streptococcus pyogenes	Penicillin G	Clindamycin
Streptococcus pneumoniae		
Penicillin-sensitive (MIC < 0.1 mg/L)	Penicillin G	Cefotaxime or ceftriaxone
Penicillin-intermediate (MIC 0.1–1 mg/L)	Cefotaxime or ceftriaxone	Fluoroquinolone, clindamycin
Penicillin-resistant (MIC ≥ 2 mg/L)	Vancomycin	Linezolid
Kingella kingae	Cefuroxime, cefotaxime, or ceftriaxone	Penicillin, ampicillin, macrolide, fluoroquinolone
Salmonella spp.	Ampicillin (if susceptible) If ampicillin resistant: cefotaxime or ceftriaxone	Ciprofloxacin
Pseudomonas aeruginosa or *Serratia marcescens*	Cefepime or piperacillin/tazobactam **AND** Gentamicin	Ceftazidime or meropenem **AND** Gentamicin
Escherichia coli	Cefotaxime or ceftriaxone	Meropenem
Pasteurella multocida	Penicillin G or ampicillin	Doxycycline Ampicillin/sulbactam
Bacteroides fragilis	Clindamycin	Metronidazole Ampicillin/sulbactam Ticarcillin/clavulanate
Neisseria gonorrhoeae	Ceftriaxone	Amoxicillin or doxycycline
Bartonella henselae	Azithromycin	Doxycycline

MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*.

home intravenous therapy are more likely to develop central venous catheter–associated complications (e.g., thromboses, infections) (Reference 44).

Although there is no clear consensus on when to change from intravenous to oral therapy, most experts recommend a transition to oral therapy on the basis of clinical markers rather than number of days of intravenous therapy. When patients show normalizing temperature, improving physical examination, and decreasing inflammatory markers (ESR and CRP), they can be changed to oral therapy.

Empiric Antimicrobial Therapy

Because the most common cause of osteomyelitis is *S. aureus*, initial empiric therapy should be targeted against this organism. Monotherapy with an antistaphylococcal agent is appropriate for patients older than 5 years with no additional risk factors (e.g., immunocompromised, sickle cell disease). For patients at risk of other organisms (e.g., *Salmonella*, *Kingella*, or *Pseudomonas*) in addition to *S. aureus*, broad-spectrum antimicrobial therapy should be initiated with an antistaphylococcal agent plus a third-generation cephalosporin.

Intravenous penicillinase-resistant penicillins (e.g., nafcillin, oxacillin) or a first-generation cephalosporin (e.g., cefazolin) has historically been considered a first-line empiric agent because of its bactericidal activity against methicillin-susceptible *S. aureus* (MSSA). However, with an increasing prevalence of CA-MRSA, it is recommended to use vancomycin (60 mg/kg/day) or clindamycin (40 mg/kg/day), both intravenously, as first-line empiric therapy until culture and sensitivity

Table 4. Antimicrobial Dosing (References 1, 15, 39, 40)

Antimicrobial Agent	Neonates		Infants and Children	Comments
	≤ 7 days	> 7 days		
Ampicillin	75–150 mg/kg/day ÷ q8h	100–200 mg/kg/day ÷ q6h	150–200 mg/kg/day ÷ q6–8h	Max single dose 2000 mg
Cefazolin	40 mg/kg/day ÷ q12h	60 mg/kg/day ÷ q8h	100 mg/kg/day ÷ q6–8h	Max single dose 2000 mg
Cefepime	100 mg/kg/day ÷ q12h	100 mg/kg/day ÷ q12h	150 mg/kg/day ÷ q8h	Max single dose 2000 mg
Cefotaxime	150 mg/kg/day ÷ q8h	150–200 mg/kg/day ÷ q6–8h	150–200 mg/kg/day ÷ q6–8h	Max single dose 2000 mg
Ceftazidime	50 mg/kg/dose q8–12h	150 mg/kg/day ÷ q8h	150 mg/kg/day ÷ q8h	Max single dose 2000 mg Potential to induce β-lactamase production
Ceftriaxone	—	—	50 mg/kg/day q24h	Max single dose 2000 mg Avoid use in the first 28 days of life
Cephalexin	—	—	100 mg/kg/day ÷ q6–8h	Max single dose 1000 mg
Ciprofloxacin	—	—	20–30 mg/kg/day ÷ q12h	
Clindamycin	15 mg/kg/day ÷ q8h	20–30 mg/kg/day ÷ q6–8h	40 mg/kg/day ÷ q6–8h (IV) 30 mg/kg/day ÷ q8h (oral)	Only for cultures with negative D-test Max oral dose: 40 mg/kg/day or 600 mg q8h
Daptomycin	—	—	6–10 mg/kg/day	
Dicloxacillin	—	—	100 mg/kg/day ÷ q6h	
Doxycycline	—	—	2-4 mg/kg/day	Only for use in patients > 8 year
Gentamicin	5 mg/kg/day ÷ q12h	5–7.5 mg/kg/day ÷ q8h	7.5 mg/kg/day ÷ q8h	Monitor peak and trough concentrations
Linezolid	10 mg/kg/dose q12h	10 mg/kg/dose q8h	10 mg/kg/dose q8h	Max dose: 600 mg twice daily
Meropenem	40 mg/kg/day ÷ q12h	60 mg/kg/day ÷ q8h	60 mg/kg/day ÷ q8h	Max single dose 2000 mg
Nafcillin	75 mg/kg/day ÷ q8h	100–150 mg/kg/day ÷ q6h	150–200 mg/kg/day ÷ q6h	Max DAILY dose 12 g
Oxacillin	150 mg/kg/day ÷ q8h	200 mg/kg/day ÷ q6h	200 mg/kg/day ÷ q6h	Max DAILY dose 12 g
Penicillin G	75,000 units/kg/day ÷ q8h	200,000 units/kg/day ÷ q6h	250,000–400,000 units/kg/day ÷ q4–6h	Max DAILY dose 24 million units
Vancomycin	15 mg/kg/dose q12h	45–60 mg/kg/day ÷ q6–8h	60 mg/kg/day ÷ q6h	Target trough concentration: 10–15 mg/L (15-20 mg/L in severe disease)

h = hours; IV = intravenous; q = every.

results are available (Reference 35). In addition, these two agents provide coverage against *S. pyogenes* and *S. pneumoniae*. According to the latest Infectious Diseases Society of America (IDSA) guidelines for the management of MRSA infections, clindamycin should only be used empirically if local resistance patterns are low (usually defined as less than 10%) and there is no evidence of bacteremia (Reference 35). Otherwise, vancomycin is preferred. In patients with a severe clinical presentation, the addition of rifampin or gentamicin to vancomycin may also be considered (Reference 45). Furthermore, vancomycin should be used as empiric therapy when other resistant gram-positive organisms (e.g., coagulase-negative staphylococci) are suspected.

Empiric therapy for neonates should cover both *S. aureus* and *Escherichia coli*. Therapy should be initiated with nafcillin or oxacillin plus cefotaxime or gentamicin. A first-generation cephalosporin (e.g., cefazolin) or clindamycin can also be considered in place of nafcillin or oxacillin for neonates. Patients with sickle cell disease should receive a third-generation cephalosporin (e.g., ceftriaxone) for coverage against *Salmonella* spp. Empiric coverage against *K. kingae* is unnecessary in most patients unless there is a high clinical suspicion such as in patients 5 years and younger who present after an upper respiratory tract infection. Figure 3 describes the empiric management of osteomyelitis in pediatric patients.

Definitive Antimicrobial Therapy

Once culture results and sensitivities are available, treatment should be directed to provide coverage against the specific organism isolated. If no organisms are identified, empiric coverage should be continued if the patient is improving. For patients who do not improve and have negative cultures, alternative or additional therapies and evaluation should be considered.

Gram-positive Organisms

Vancomycin is the treatment of choice for MRSA osteomyelitis, especially for strains that are not susceptible to clindamycin and in critically ill patients. However, dosing vancomycin at 40 mg/kg/day is inadequate to achieve the pharmacokinetic and pharmacodynamic targets recently proposed for adults. An area under the curve/minimum inhibitory concentration (AUC/MIC) ratio of 400 or more in adults with MRSA bacteremia or pneumonia correlates to positive treatment outcomes (Reference 35). Trough levels of 15–20 mg/L are recommended for invasive MRSA infections in adults, including osteomyelitis, because they correlate to an AUC/MIC ratio of 400 or more, increase tissue penetration, and minimize the selection of resistant strains of MRSA (Reference 35). Doses of at least 60 mg/kg/day should be initiated in children to attain these trough targets, particularly in severe cases (e.g., with concurrent bacteremia), even though data are limited on the efficacy and safety of these serum levels in children (References 38, 46). It is important to achieve adequate vancomycin serum concentrations early in therapy to ensure a faster transition to oral therapy (Reference 47).

Clindamycin is an attractive option for CA-MRSA osteomyelitis because of its high bone concentrations; its efficacy, which is close to 100% (in the absence of inducible resistance); and its availability in both intravenous

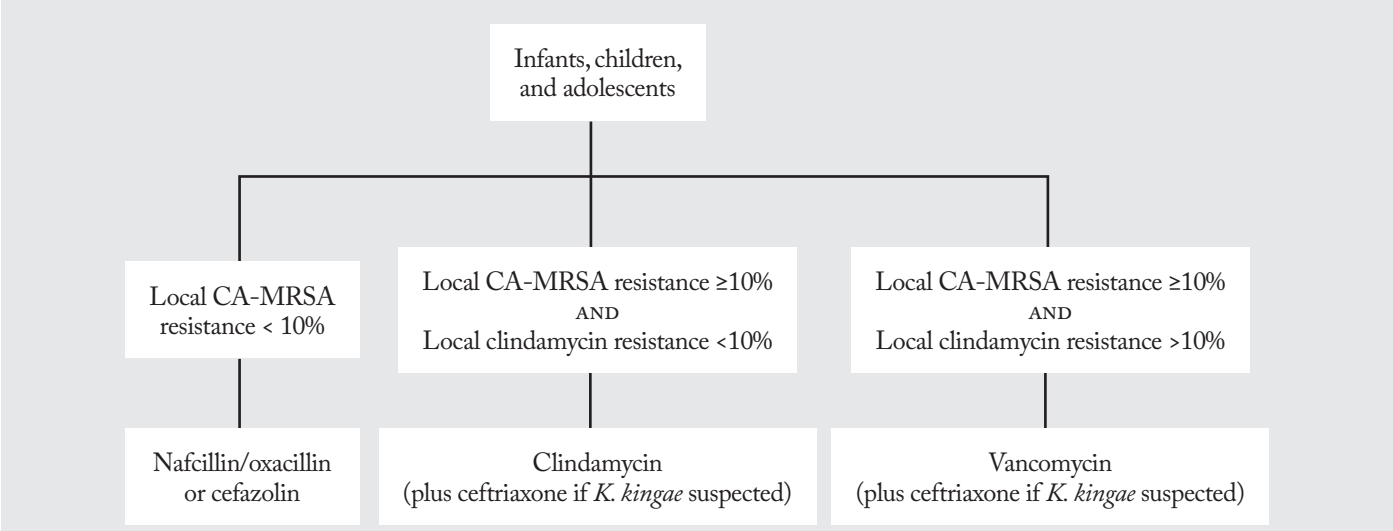


Figure 3. Empiric treatment algorithm for acute hematogenous osteomyelitis for infants, children, and adolescents.

CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*.

and oral preparations (References 48–51). Clindamycin also has good activity against toxin-producing gram-positive organisms. The double-disk diffusion (D-test) is an important molecular test for the confirmation of inducible-resistant CA-MRSA strains (Reference 52) (Figure 4). This test identifies inducible clindamycin resistance among strains that initially show susceptibility to clindamycin. Clindamycin is a lincosamide antibiotic similar to the macrolide class of antibiotics. The practitioner should be aware of the potential for inducible resistance when a MRSA isolate shows clindamycin susceptibility and erythromycin resistance. The D-test is performed by creating a lawn of bacteria on an agar plate and placing a clindamycin and erythromycin disk 15 mm apart on the plate. If there is a uniform zone of inhibition around the clindamycin disk, then the test is negative (i.e., no inducible resistance). If there is blunting of the zone of inhibition on the side closest to the erythromycin disk that produced a D shape, then the test is positive (i.e., inducible resistance). For a positive D-test, the potential for treatment failure is increased, and clindamycin therapy should not be used. In an era of increasingly resistant gram-positive organisms, including vancomycin-intermediate and vancomycin-resistant staphylococci, clinical evidence is limited for the use of daptomycin and linezolid in pediatric osteomyelitis. These agents are not typically used for empiric therapy. Once culture results are known, they should be considered alternative therapy for MRSA osteomyelitis in patients who cannot receive vancomycin or clindamycin (Reference 35).

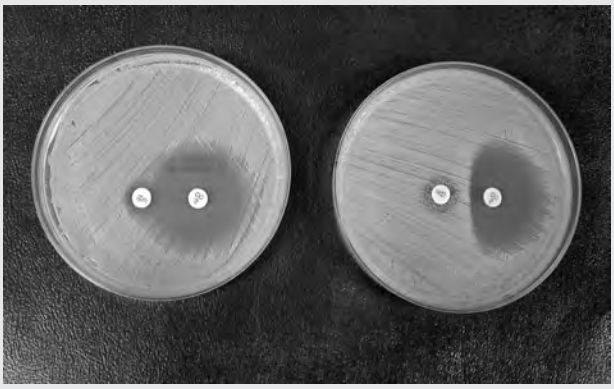


Figure 4. The D-test. A negative D-test is shown on the left, and a positive D-test is shown on the right. The erythromycin disk is located on the left of each agar plate, and the clindamycin disk is located on the right.

D-test = double-disk diffusion.
Photo courtesy of Hixson-Wallace J.

Daptomycin is a lipopeptide antibiotic with bactericidal activity against sensitive and resistant gram-positive organisms. It is an option for osteomyelitis treatment as a parenteral alternative to vancomycin (Reference 35). Evidence in children is limited; however, it has been found to be about 90% effective in adults for the treatment of osteomyelitis (References 53, 54). Daptomycin may have a role in the management of chronic osteomyelitis because of its ability to penetrate biofilm (Reference 26). Daptomycin should not be used in the setting of osteomyelitis with concomitant pneumonia because it is inactivated by alveolar surfactants.

Linezolid is an oxazolidinone antibiotic with activity against MRSA and other resistant gram-positive organisms. Linezolid achieves high bone concentrations and inhibits toxins produced by gram-positive bacteria (References 55, 56). Linezolid is approved for use in pediatric patients, including neonates, and is available in intravenous and oral formulations with around 100% oral bioavailability. Therefore, transitioning patients to oral therapy can be considered early in the treatment course. Linezolid was reported to be effective (85% complete recovery) and safe for pediatric patients with osteomyelitis in a case series and one large clinical trial (References 57, 58).

If MSSA is identified, patients who were empirically initiated on vancomycin or clindamycin should change to a penicillinase-resistant penicillin or cefazolin. There is greater bactericidal activity against MSSA with the penicillinase-resistant penicillins than with vancomycin (Reference 59). Cefazolin can be administered less frequently (every 8 hours) than either nafcillin or oxacillin (every 6 hours), which can be advantageous for outpatient use. In addition, there is a potential for thrombophlebitis with intravenous nafcillin administration. In patients with a serious hypersensitivity reaction to penicillin and a positive MSSA culture, clindamycin is the treatment of choice. Penicillin, clindamycin, or vancomycin may be used, depending on patient characteristics and microbial sensitivities to these agents, for the treatment of streptococcal species (e.g., *S. pyogenes* and *S. pneumoniae*).

Gram-negative Organisms

K. kingae, if identified, can be treated with a β-lactam antibiotic such as a second- or third-generation cephalosporin. Alternative agents include penicillin, ampicillin, macrolides, or ciprofloxacin. Clindamycin should not be used if the organism is inherently resistant. If *E. coli* is identified as the cause of osteomyelitis, therapy should be guided by the susceptibility results, with the empiric agent continued (e.g., cefotaxime) if clinical improvement has been documented and the bacterial strain is susceptible. A complete list of bacteria-specific therapy is provided in Table 3.

First-line treatment of *Salmonella* is ampicillin if the organism is susceptible. For resistant strains, a third-generation cephalosporin (e.g., cefotaxime, ceftriaxone) should be used. Fluoroquinolones (e.g., ciprofloxacin) are an alternative in patients with *Salmonella* osteomyelitis but are usually reserved for patients allergic to β-lactam antibiotics and as oral step-down therapy.

Pseudomonas aeruginosa is not a common organism in pediatric osteomyelitis, but if identified, therapy should include an antipseudomonal cephalosporin (e.g., ceftazidime, cefepime), antipseudomonal penicillin (e.g., piperacillin/tazobactam), or carbapenem (e.g., meropenem). Combination therapy with an antipseudomonal penicillin, carbapenem, or cephalosporin and an aminoglycoside may be considered in severe cases or with multidrug-resistant strains. The current American Academy of Pediatrics guidelines on the use of systemic fluoroquinolones in pediatric patients state that these agents can be used for definitive cases of acute or chronic osteomyelitis caused by *P. aeruginosa* (Reference 60).

For an anaerobic infection, therapy can be continued with clindamycin if it was initiated as an empiric agent. Metronidazole, ampicillin/sulbactam, and ticarcillin/clavulanate are alternative agents with anaerobic activity.

Role of Oral Antimicrobial Therapy

Oral antibiotics play a very important role in the medical management of pediatric patients with osteomyelitis. Oral therapy is usually initiated after adequate treatment of intravenous therapy, depending on the severity of the infection and the clinical response of the patient. Oral antibiotics can also be used as first-line agents in mild infections, but this is less common. Important considerations when initiating oral antibiotic therapy for the treatment of osteomyelitis in children include palatability, cost, availability of appropriate dosage forms, and ease of administration (Reference 47). All of these characteristics are crucial in ensuring medication adherence for the treatment duration.

The most frequently used oral antibiotics in pediatric patients with osteomyelitis include clindamycin, linezolid, cephalexin, and dicloxacillin. Trimethoprim/sulfamethoxazole, doxycycline, or minocycline—alone or in combination with rifampin—and fluoroquinolones may also be considered, although data are limited. Trimethoprim/sulfamethoxazole has excellent activity against CA-MRSA and good oral palatability. Because of the risk of dental staining in younger children, tetracyclines can be used for CA-MRSA infections in patients after 8 years of age. Table 3 lists oral alternatives for the most common intravenous therapies. Patients should be initiated on oral therapy before discharge to ensure adherence to the selected therapy. Both clindamycin and linezolid have excellent oral bioavailability but poor palatability (Reference 61). Oral β-lactam antibiotics must be given at high doses to achieve adequate bone penetration. Dosing is typically 2–3 times higher than recommended for other infections.

Outpatient Parenteral Antimicrobial Therapy

Although sequential intravenous to oral therapy is the preferred treatment of osteomyelitis, intravenous therapy must sometimes be continued for an extended period. Candidates for home parenteral therapy include the following: neonates, patients with infections caused by organisms when there is no oral alternative, patients who cannot tolerate oral therapy, patients with chronic osteomyelitis, immunocompromised patients, patients with sickle cell anemia who have poor blood flow to the local area of infection, and patients in whom poor adherence to oral therapy is suspected (Reference 62). In these cases, patients must have an indwelling central venous catheter inserted to continue intravenous therapy as an outpatient. Coordination for home parenteral therapy requires an interprofessional approach using the physician, caregiver, pharmacist, and nurse. Educating the caregiver is essential to preventing possible complications from home intravenous therapy, including catheter-related bacteremia and line malfunction.

Outpatient parenteral antimicrobial therapy for osteomyelitis can decrease health care costs associated with this infection by reducing the number of hospital days and possible exposure to additional hospital pathogens. However, this approach may affect patient and family quality of life because it may be associated with increased cost to the family and considerably affect the child's ability to attend school or perform daily activities. Both the benefits and possible risks and disadvantages need to be considered when selecting patients for outpatient parenteral therapy.

Localized Antibiotic Therapy

Localized antibiotic delivery directly to the infected bone provides the advantage of high local concentrations of the antibiotic with limited systemic toxicity. Cement beads made of polymethylmethacrylate (PMMA) are impregnated with antibiotics to allow drug release over several weeks to months (Reference 63). These beads must be surgically placed at initiation and removed upon therapy completion. Antibiotic-impregnated cement beads can be used in patients with difficult-to-treat infections and those with chronic osteomyelitis. They can be used in combination with systemic antibiotics or as an alternative. Antibiotics that have been used in this capacity include gentamicin,

vancomycin, penicillins, and cephalosporins. There is in vitro evidence with daptomycin in PMMA beads and in calcium sulfate, which is another localized delivery matrix (Reference 64).

Nonpharmacologic Therapy

Nonpharmacologic therapy includes surgical debridement and the use of hyperbaric oxygen. Surgical debridement of the infected bone and drainage of adjacent soft tissue abscesses is a first-line treatment in addition to appropriate empiric antimicrobial therapy. Surgical drainage allows direct examination of the infected area and, if debridement of bone occurs, direct histopathologic examination of the bone. This can help guide decisions about appropriate antimicrobial therapy. Some patients with CA-MRSA may require several incision and drainage procedures during the course of therapy.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy is used as an adjunctive treatment to surgery and antibiotics in patients with chronic osteomyelitis that is refractory to standard therapy. The procedure requires placement of the patient in an enclosed chamber where oxygen pressure is greater than sea level. The increased oxygen pressure enhances oxygen delivery to the infection site, leading to the formation of new capillaries, increased transport of antibiotics to the infected area, formation of a collagen matrix, suppression of anaerobic bacteria, and increased ability of phagocytes to target bacteria (Reference 65). Disadvantages of this treatment approach include limited clinical experience in pediatric patients, increased cost, and adverse effects, such as barotraumas and reversible myopia.

Monitoring Parameters

Because patients with osteomyelitis will require prolonged antibiotic therapy, it is very important that they be closely monitored throughout the treatment. Once the initial antimicrobial therapy is started, improvements in clinical signs and symptoms should occur within 48–72 hours. Patients should be monitored for clinical and laboratory response to therapy, especially when no organism is identified and for the presence of adverse drug reactions and adherence to outpatient therapy. Laboratory parameters important for monitoring therapeutic response include culture and sensitivity results, improvement in markers of inflammation (e.g., CRP, ESR), and decrease in WBC. In patients with positive blood cultures, repeat cultures should be obtained to ensure eradication of the bacteremia. Patients receiving outpatient therapy should be monitored weekly for normalization of CRP and to ensure no toxicity is associated with the treatment. After 4–6 weeks of appropriate antimicrobial therapy, success can be defined by the resolution of clinical signs and symptoms and normalization of all laboratory tests.

Common adverse reactions in patients receiving β-lactam antibiotics include diarrhea and gastrointestinal upset. Patients receiving β-lactam antibiotics should be monitored closely for the development of a rash or other allergic reaction (e.g., urticaria). Clindamycin causes gastrointestinal upset, diarrhea (that may develop into pseudomembranous colitis), and nausea. Patients and their caregivers should be counseled on contacting their provider if diarrhea becomes severe or if bloody stools develop. Renal function should be monitored weekly in patients receiving vancomycin, and patients should be monitored for the development of red man syndrome on initiation of therapy. If red man syndrome occurs, the infusion can be extended for a longer period (2 hours vs. 1 hour), and diphenhydramine can be administered before the infusion. Creatinine phosphokinase levels should be monitored routinely in patients receiving daptomycin because rhabdomyolysis is associated with increased drug serum levels. Caution is advised with the use of linezolid for more than 2 weeks because of treatment duration–related adverse effects (e.g., thrombocytopenia, peripheral neuropathies, optic neuritis) (References 35, 66). It is recommended to obtain weekly complete blood cell counts in patients receiving linezolid longer than 2 weeks and an ophthalmologic evaluation if therapy is continued for greater than 4 weeks. However, some data suggest that the hematologic effects of linezolid occur less frequently in children than in adults, especially in the first 2 weeks of therapy (Reference 67).

Infectious Arthritis

Infectious arthritis, commonly referred to as pyogenic or septic arthritis, is defined as an infection of the joint. It is much more common in pediatric patients than osteomyelitis. The infection usually begins in a monoarticular joint with inflammation of the joint space, synovium, synovial fluid, and surrounding cartilage. Prompt diagnosis and treatment is crucial in any patient with suspected infectious arthritis to prevent joint damage or spread of the infection to surrounding tissue or bone. In rare cases, if left untreated, the disease can be fatal. Many of the concepts previously introduced for osteomyelitis (most common organisms, treatments) also apply to infectious arthritis.

Epidemiology

The incidence of infectious arthritis is between 5 and 12 cases per 100,000 children; however, the incidence varies by age (Reference 68). Children younger than 3 years and adolescents have the highest incidence (Reference

1). Males are affected twice as often as females, perhaps because males have more traumatic injuries during childhood. Infectious arthritis in children is almost exclusively from hematogenous spread and typically involves only one joint. The most common sites of infectious arthritis are the hip and knee, followed by the ankle (Reference 68). The hip is most commonly affected in neonates and infants. Infections of the upper extremities are less common, with the elbow and shoulder being reported in less than 10% of cases (References 69).

Although most cases of infectious arthritis are acute in nature, both chronic monoarticular arthritis and polyarticular arthritis can also occur. Mycobacteria, *B. burgdorferi*, and fungi typically present as chronic monoarticular arthritis. Polyarticular arthritis is most common after a viral infection.

Pathophysiology

Infectious arthritis occurs secondarily to hematogenous seeding of an organism within the joint space. The synovial membrane is infected first. Edema and hypertrophy in the adjacent joint space lead to accumulation of exudative fluid in the synovium. Neutrophils, cytokines, and proteolytic enzymes are then recruited to the infection site. Pus accumulates in the joint space and leads to destruction of cartilage. Children younger than 18 months can develop infectious arthritis secondary to a bone infection because of the presence of transphyseal blood vessels that extend from the metaphysis to the epiphysis and growth plate (Reference 1).

Microorganisms

Bacteria are the most common cause of infectious arthritis, whereas fungi and mycobacteria are rarer. Bacterial infectious arthritis is commonly classified into nongonococcal or gonococcal etiologies. Gram-positive organisms are most commonly identified in nongonococcal cases. Pediatric patients can also develop reactive arthritis in a joint after infection at a distant site in the body.

S. aureus is the most common bacterial cause of infectious arthritis in all age groups, followed by *S. pyogenes* and *K. kingae*. Similar to osteomyelitis, CA-MRSA strains have emerged as a common pathogen isolated from patients with infectious arthritis, but rates vary geographically. One small study of 45 patients in Texas found that one-third of isolates were positive for MRSA (Reference 70). Strains of *S. aureus* associated with the PVL gene are associated with more severe disease (e.g., CRP of 10 mg/dL or greater, longer duration of fever), the presence of concomitant abscess or cellulitis, and the possibility of a more difficult-to-treat infection (Reference 71).

In neonates and infants younger than 2 months, common causes also include group B streptococci, *Neisseria gonorrhoeae*, gram-negative enteric bacteria (e.g., *E. coli*), and, rarely, *Candida*. *S. aureus*, *S. pneumoniae*, *S. pyogenes,* and *K. kingae* are the most common organisms seen in children 2 months to 5 years of age. Because of the increase in Hib immunization rates during the past decade, this organism is now a rare cause of septic arthritis in an immunized child.

The most common cause of infectious arthritis in sexually active adolescents is *N. gonorrhoeae*. Other rare causes include *B. burgdorferi* (i.e., patients with tick exposure while in endemic areas), *Mycobacterium tuberculosis*, viruses (e.g., parvovirus B19, varicella, hepatitis B), and fungi.

Reactive arthritis is commonly seen in patients with gastrointestinal tract infections caused by *Salmonella*, *Shigella*, *Campylobacter*, or *Yersinia enterocolitis* or with genitourinary tract infections caused by *Chlamydia trachomatis* or *N. gonorrhoeae*. It may also occur after a group A streptococcal infection.

Risk Factors

Risk factors are associated with either systemic or host factors, such as age (younger than 3 years), preexisting joint disease, or immunosuppression. Local risk factors include recent joint trauma or surgery, presence of prosthetic joints, puncture wounds, recent administration of intra-articular corticosteroids, and rheumatoid arthritis. Although less common in the general pediatric population, intravenous drug abusers are also at increased risk of developing infectious arthritis.

Clinical Presentation and Diagnosis

Signs and Symptoms

Patients with infectious arthritis typically present with an acute systemic infection. Fever, chills, and malaise are common symptoms. The joint is painful, hot, and edematous. It is important to distinguish patients with infectious causes of arthritis from those who have other causes. Transient synovitis is the most common cause of hip pain in children 5–10 years of age. Although no exact cause is known, transient synovitis has been associated with trauma, preceding viral infections, and vaccine-mediated reactions (Reference 1). The most common clinical presentation in these patients is unilateral pain and decreased range of motion. The patient may be afebrile or present with a low-grade fever. Other causes of joint pain (e.g., juvenile idiopathic arthritis, trauma, malignancy) should be considered if an infectious source cannot be identified.

Diagnostic Criteria

Clinical presentation is considered the gold standard diagnostic tool for infectious arthritis (Reference 72). Other diagnostic approaches include aspiration of the synovial fluid, radiography, ultrasonography, and MRI. The synovial fluid should be collected for culture and

sensitivity in any patient with a clinical presentation consistent with infectious arthritis. Typical findings suggestive of infectious arthritis upon analysis of joint fluid include isolation of bacteria on the Gram stain, leukocytosis (50,000/mm^3 or greater), decreased glucose (less than 50% of serum glucose), and increased lactate dehydrogenase, protein, or lactic acid. In addition, blood cultures should be performed to determine the presence of bacteremia. Additional laboratory findings that may suggest infectious arthritis include an increased WBC or increased inflammatory markers (e.g., ESR and CRP). Studies have shown the ESR and CRP to be elevated during septic arthritis in around 95% and 90% of patients, respectively (Reference 73). About 30% to 40% of patients will also have a positive blood culture (Reference 68).

Radiography is performed to rule out trauma or malignancy. A radiograph is useful in identifying whether there are significant abnormalities on the adjacent bones to suggest the presence of a concomitant osteomyelitis. Ultrasonography is used to determine the presence of fluid within the joint space and can guide in joint aspiration. However, ultrasonography cannot discern whether fluid within the joint space is infected. An MRI should be considered for patients with suspected concomitant osteomyelitis.

Course and Prognosis

The overall prognosis is favorable for infectious arthritis with prompt initiation of antimicrobial therapy and adequate drainage. Infections of the hip are associated with the highest rates of long-term sequelae. Complications of infectious arthritis include abnormal bone growth, bony deformities at the femoral or humeral head, and local cartilage destruction. These occur more commonly in neonatal patients, patients with adjacent osteomyelitis, patients who do not seek immediate medical care after initiation of symptoms, and patients with *S. aureus*, including both MSSA and MRSA. If diagnosis is made promptly, the incidence of long-term sequelae after infectious arthritis is much lower.

Treatment

The goals of therapy for infectious arthritis include eradicating the infecting organism, resolving the infection and inflammation, and preventing long-term sequelae. Treatment of infectious arthritis is very similar to that of osteomyelitis because of the similarity of causative organisms. However, considerations should be made for patient-specific age, risk factors, and other disease-related issues. Once culture and sensitivity results are available, therapy can be tailored to the specific organism.

The recommended duration of antibiotic therapy for septic arthritis is 3–4 weeks (Reference 35). A sequential intravenous to oral therapy approach is similar to that for osteomyelitis. Studies have shown similar outcomes in patients treated with shorter courses of intravenous therapy (7 days or less) compared with prolonged courses (more than 10 days) for the treatment of infectious arthritis. Patients may be changed to oral therapy once they have been afebrile for at least 24 hours, the joint swelling has improved to allow better range of motion, and the CRP is decreasing (References 74, 75). Once oral therapy is initiated, the highest recommended weight-based doses per day are required to achieve adequate joint tissue concentrations (Reference 76).

Pharmacologic Therapy

Empiric therapy should target *S. aureus* and usually includes vancomycin or intravenous clindamycin to provide coverage against MRSA. If *K. kingae* is strongly suggested (age younger than 5 years, preceding upper respiratory infection), a β-lactam antibiotic (e.g., penicillin or cephalosporin) should be added to vancomycin or clindamycin (Reference 77). Therapy for sexually active adolescents should include ceftriaxone to cover *N. gonorrhoeae* in addition to staphylococcal coverage. When culture and sensitivity results are available, treatment should be directed at the specific bacteria isolated from the joint fluid. Table 4 lists the most common organisms and corresponding antimicrobial therapy for infectious arthritis. Intra-articular antibiotics are not indicated for the management of infectious arthritis. One small study showed benefit in reducing long-term complications with the addition of dexamethasone to standard antibiotic therapy (Reference 78). More research is required before this approach can be routinely recommended.

Nonpharmacologic Therapy

First-line therapy in the management of infectious arthritis is joint aspiration. This strategy is even more crucial than antimicrobial therapy to provide positive clinical outcomes. Closed-needle aspiration of the joint is indicated for all joints except the hip and shoulder, which require open drainage. Joint drainage can be repeated daily for 5–7 days. An alternative to needle aspiration is arthroscopy with placement of a drainage tube. Joint aspiration and drainage should always be performed in conjunction with antibiotic therapy. Aspiration not only aids in diagnosis but also helps in the therapeutic management of these patients. Antimicrobial therapy should be initiated, if possible, after joint aspiration. Parameters to monitor after joint drainage include the volume of synovial fluid and the presence of WBCs, which should decrease with each subsequent drainage.

Monitoring Parameters

The key monitoring parameters in the management of infectious arthritis include laboratory and inflammatory markers and clinical signs and symptoms, particularly improvement in joint movement, and adherence to antimicrobial therapy. Routine monitoring of CRP is suggested to follow response to therapy. Patients may be safely transitioned to oral therapy once the CRP normalizes, even in the presence of continued fever. If CRP has not decreased after adequate microbial coverage for 72 hours, further studies are warranted to ensure appropriate drainage has occurred.

Conclusions

Bone and joint infections are common causes of invasive infections in the pediatric population. *S. aureus* remains the most common causative organism in both osteomyelitis and infectious arthritis, with an increasing incidence of CA-MRSA seen in recent years. Prompt identification of bone or joint infection and prompt initiation of appropriate empiric antimicrobial therapy are keys in the management of these infections. Treatment courses are typically prolonged, 3–4 weeks for infectious arthritis and 4–6 weeks for osteomyelitis, with an early transition to oral antibiotic therapy becoming the standard of care. The management of these infections requires a multidisciplinary approach including infectious disease physicians, nurses, physical therapists, pharmacists, and surgeons. Pharmacists play a crucial role in assisting with determining cost-effective therapies, transitioning patients to appropriate oral therapy, ensuring adherence to outpatient therapy, monitoring for medication toxicities and adverse drug reactions, and assisting with discharge planning.

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CHAPTER 41

Skin and Soft Tissue Infections of Bacterial and Viral Etiology

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Learning Objectives

1. Recognize common bacterial and viral skin and soft tissue infections (SSTIs) of childhood through an understanding of their definitions, epidemiology, and clinical presentation.
2. Select empiric and definitive antimicrobial therapy on the basis of the etiologic agent, antimicrobial resistance patterns, severity of illness, and clinical evidence.
3. Recommend supportive treatment to aid in the recovery from active illness, and preventive strategies for avoiding disease transmission and outbreaks.
4. Recognize the increasing prevalence of community-associated methicillin-resistant *Staphylococcus aureus* as a pathogen in pediatric SSTIs and its impact on antibiotic selection.
5. Monitor antimicrobial therapy to maximize effectiveness and safety.

Abbreviations in This Chapter

BI	Bullous impetigo
CA-MRSA	Community-associated methicillin-resistant *Staphylococcus aureus*
GAS	Group A β-hemolytic *Streptococcus*
HA-MRSA	Hospital-acquired methicillin-resistant *Staphylococcus aureus*
HFMD	Hand, foot, and mouth disease
HHV	Human herpes virus
HSV	Herpes simplex virus
IC	Impetigo contagiosa
IVIG	Intravenous immunoglobulin
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-sensitive *Staphylococcus aureus*
NF	Necrotizing fasciitis
OC	Orbital cellulitis
PC	Periorbital cellulitis
SSSS	Staphylococcal scalded skin syndrome
SSTI	Skin and soft tissue infection
TMP/SMX	Trimethoprim/sulfamethoxazole
VZV	Varicella zoster virus

Introduction

Skin and soft tissue infections (SSTIs), a common reason for children to seek medical attention, can range from a localized, superficial folliculitis, easily managed as an outpatient, to a life-threatening necrotizing fasciitis (NF), requiring immediate surgical intervention (Figure 1). Failure to quickly control a localized infection or identify symptoms suggestive of a deep tissue source can result in disseminated disease and significant morbidity. Therefore, pharmacists should be familiar with the clinical presentation of common skin lesions so that they can refer patients to seek further treatment when necessary. Diagnosing superficial skin infections in an ambulatory setting can be difficult because of their clinical similarities to other inflammatory diseases and challenges in histologic or microbiologic analysis (e.g., turnaround time, difficulty obtaining good-quality samples). A detailed history, time course, and physical examination are essential in making the proper diagnosis. Pharmacologic treatment is often empiric, requiring a general knowledge of common pathogens and local resistance patterns to antibiotics.

This chapter aims to provide an overview of the diagnosis and management of common bacterial and viral SSTIs encountered in children. A discussion of fungal dermatologic conditions is beyond the scope of this chapter; thus, the reader is referred elsewhere in this book.

Superficial Bacterial Skin Infections

Historically, the most common pathogens responsible for SSTIs are Staphylococcus aureus and group A β-hemolytic *Streptococcus* (*Streptococcus* pyogenes) (GAS). In recent years, an increasing prevalence of community-associated methicillin-resistant *S. aureus* (CA-MRSA) has been observed in SSTIs. Community-associated methicillin-resistant *S. aureus* differs from hospital-acquired MRSA (HA-MRSA) in several ways. First, CA-MRSA affects populations not historically at risk of nosocomial infections (e.g., previously healthy children). Second, *S. aureus* resistance to methicillin is conferred by an alteration in the penicillin-binding protein PBP2, which is encoded on the mecA gene complex of the staphylococcal cassette chromosome mec (SCCmec). Shorter-length SCCmec subtypes carried by CA-MRSA compared with HA-MRSA encode

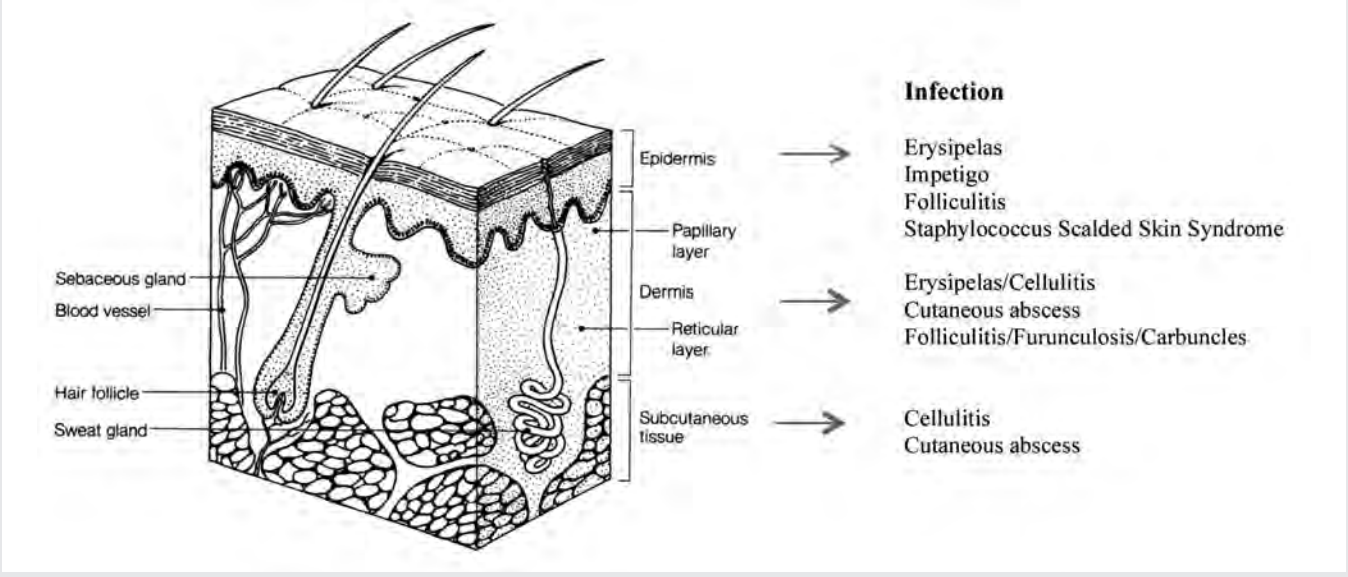


Figure 1. Schematic of skin structure and sites of superficial bacterial infections.

fewer proteins that produce antibiotic resistance, making CA-MRSA isolates less prone to developing multidrug resistance. Another unique molecular feature of CA-MRSA is the expression of a virulence factor, Panton-Valentine leukocidin (PVL), which can cause tissue necrosis and leukocyte destruction. This may partly explain the high association of CA-MRSA with pustular SSTIs such as furuncles, purulent cellulitis, and cutaneous abscesses.

Folliculitis, Furuncles, and Carbuncles

Folliculitis, furuncles, and carbuncles are a family of pyodermic infections that originate around a hair follicle. Folliculitis is the most superficial and least extensive of the three, resulting in the formation of a small follicular abscess in the epidermis. Furuncles (or boils) are characterized by a more widespread inflammatory response of adjacent follicles extending into the dermis and subcutaneous tissue. These suppurative lesions are painful, erythematous, fluctuant, and may cause cellulitis in the surrounding areas. Carbuncles represent a confluence of furuncles with still-wider infiltration that can spontaneously drain from multiple sites (References 1–3).

Children of all age groups can develop folliculitis. Furunculosis tends to occur in adolescents, whereas carbuncles are generally seen in adulthood (Reference 2). Risk factors include hyperhidrosis, obesity, diabetes, seborrhea, anemia, malnutrition, and immunodeficiency. Clusters of infections may occur in people who interact in close quarters, especially in settings where skin injury is common, or in those who share household items that can transfer infectious material (Reference 1).

Microbiologic Etiology

S. aureus is the most common causative agent of all three infections, and CA-MRSA now accounts for 3% to 25% of folliculitis (Reference 4). Genes for the virulence factor PVL have been detected in 42% of furuncles caused by *S. aureus*, specifically those associated with epidemic disease (Reference 5). Colonization with *S. aureus* is likely a risk factor for recurrent infection because nasal carriage rates are twice as high in patients with recurrent infection as in the general population (Reference 5). Gram-negative folliculitis with *Klebsiella* spp., *Enterobacter* spp., and *Proteus* spp. typically presents on the faces of patients with a history of antibiotic therapy for acne (Reference 1). "Hot tub" folliculitis is contracted through exposure to *Pseudomonas aeruginosa* from a contaminated hot tub or whirlpool.

Clinical Presentation

Folliculitis occurs in hair-bearing areas and typically arises with no preexisting trauma to the skin. Inflammation along the hair shaft causes swelling and erythema that is accompanied by the formation of small dome-shaped pustules. Sites commonly affected include the scalp, extremities, buttocks, and areas of skin prone to moisture and friction (Figure 2). Furuncles and carbuncles can present as fluctuant masses that drain spontaneously, and often, they are accompanied by constitutional symptoms, such as fever and malaise. These infections are most often seen on the neck, breasts, face, buttocks, axillae, and groin (Reference 2).



Figure 2. Staphylococcal folliculitis on the buttocks where the lesions have been excoriated. Images reprinted with permission from Medscape.com, 2011.

Diagnosis

The diagnosis of these conditions is largely based on clinical appearance. Cultures are not routinely obtained, but drainage from a lesion or abscess may undergo Gram staining and analysis when it is necessary to identify the causative organism.

Treatment

Most folliculitis cases will resolve spontaneously, but complicated follicular infections should be treated with a short course of oral antibiotics targeting *S. aureus*. Cephalexin and dicloxacillin are recommended for methicillin-sensitive *S. aureus* (MSSA) coverage. Empiric coverage for CA-MRSA is recommended in communities where the local prevalence exceeds 10% (Reference 6); treatment options include trimethoprim/sulfamethoxazole (TMP/SMX) (in children at least 2 months of age to minimize the potential for bilirubin displacement from albumin and hence increase the risk of kernicterus), doxycycline (in children at least 8 years of age to minimize potential interference with tooth and bone formation), or clindamycin. Inducible resistance to clindamycin should be ruled out with a D-test before it is initiated. If local resistance patterns are greater than 10% to 15%, clindamycin should be avoided (References 6, 7).

Prompt therapy for furuncles and carbuncles is important to prevent dissemination into deep tissues or other organs. Warm, moist compresses can be applied to lesions to encourage wound drainage, and loculations within connective masses should be gently incised to ensure the complete evacuation of purulent material. Parenteral antibiotics are rarely indicated; however, patients presenting with severe systemic symptoms should be treated initially with a parenteral penicillinase-resistant penicillin (e.g., oxacillin, nafcillin) or a first-generation cephalosporin and then converted to oral therapy for 7–10 days. Empiric vancomycin should be considered in all critically ill patients, especially those living in communities where CA-MRSA prevalence is high.

Treatments of chronic dermatologic conditions that predispose a patient to secondary bacterial infections and improvements in daily hygiene (e.g., antiseptic body washes, one-time use of washcloths, frequent dressing changes of draining lesions) are essential for preventing outbreaks. Topical anti-infectives such as chlorhexidine are most effective when used in conjunction with other strategies; however, the risk of adverse neurologic effects should preclude the use of hexachlorophene in children younger than 2 months (Reference 7). Dilute bleach baths given twice daily for 15 minutes may eradicate skin colonization of methicillin-resistant *S. aureus* (MRSA), but they should only be administered with clear instructions. Decolonization strategies with nasal mupirocin and oral rifampin can help reduce *S. aureus* nasal colonization, although their efficacy in preventing disease recurrence and impact on antimicrobial resistance is unclear (Reference 7). Current recommendations of the Infectious Diseases Society of America (IDSA) include the use of mupirocin alone for 5–10 days or in combination with a topical antiseptic for topical decolonization. In severe recurrent infection, rifampin together with TMP/SMX or doxycycline for 5–10 days is recommended.

Erysipelas and Cellulitis

Erysipelas and cellulitis are diffuse, spreading skin infections without a suppurative focus. Erysipelas infection involves the epidermis, dermis, and occasionally lymphatic system. Because of its proximity to the skin surface, erysipelas is characterized by intense erythema and sharply demarcated, palpable borders. The disease can affect individuals across all racial and socioeconomic groups; it is commonly seen among the very young and very elderly. Neonates and young children are particularly at risk in the pediatric age group. Immunosuppression is a risk factor for disease.

In contrast, cellulitis predominantly affects deep layers of the skin such as the dermis and cutaneous tissue. It is manifested by generalized areas of edema, erythema, warmth, and tenderness without distinct margins (References 1, 3, 8). Cellulitis is a common reason for clinic visits in the United States, accounting in one study for 2.2% of all office visits to general practitioners (Reference 9). Infection can occur through the inoculation of a pathogen at a site of minor skin trauma or secondary

to conditions such as a compromised cutaneous barrier, recent surgical procedure, penetrating trauma from intravenous drug use or animal bites, impaired lymphatic drainage, or immunosuppression (Reference 7).

Microbiologic Etiology

Group A β-hemolytic *Streptococcus*, or *S. pyogenes*, is the most common cause of erysipelas, though groups B, C, and G have also been implicated. Other rare etiologies such as *S. aureus, Klebsiella pneumoniae, Yersinia enterocolitica,* and *Haemophilus influenzae* should be considered, especially in immunocompromised patients or those not responding to empiric anti-streptococcal therapy (Reference 8).

Historically, most cellulitis cases have been caused by GAS and *S. aureus*. A recent systematic review of patients presenting with uncomplicated, nonsuppurative cellulitis who underwent confirmatory tests (e.g., needle aspiration or punch biopsy) confirmed this observation (Reference 10). The proportion of staphylococcal isolates that were MRSA was not quantified in this study. The contribution of MRSA relative to GAS and MSSA in nonpurulent cellulitis remains unknown; however, in cellulitis cases complicated by abscess formation, CA-MRSA should be strongly suspected, given its high prevalence as reported in epidemiologic studies of purulent SSTIs (Reference 7).

Clinical Presentation

Erysipelas usually originates from a minor skin trauma that becomes inoculated with a pathogen. A small red patch may rapidly develop streaking and induration as the lymphatic system becomes involved. The affected area, which is exquisitely tender and sharply demarcated, can advance rapidly and further progress to bullae formation with severe necrosis. In general, patients are not toxic appearing, and they lack systemic symptoms such as fever. The most common infection sites are the face (in a butterfly distribution) and lower extremities (legs and feet), though in neonates, the periumbilical area is often the primary infection site (References 1, 11).

Bacterial cellulitis represents an inflammatory process in solid tissues, with typical findings of redness, warmth, pain, and swelling, but without suppuration or necrosis (Reference 2). Although most patients show no signs of systemic illness, severe cases of cellulitis can be accompanied by fever, hemodynamic instability, and regional lymphadenopathy, together with eruptions of petechiae, vesicles, and bullae. Common infection sites in children are the lower extremities, face, periorbital area, and perineum (References 2, 12). Complications from deeply disseminated cellulitis may result in osteomyelitis and septic arthritis (Reference 1).

Diagnosis

The diagnosis of erysipelas is largely based on the clinical appearance of the skin. Laboratory assessment may show an elevated leukocyte count with polymorphonuclear predominance, though blood cultures are only positive in 5% of cases (Reference 13). Needle aspirations of the lesion should be performed at the advancing margin or at the initiating wound if an abscess is present (Reference 1).

Cellulitis is often diagnosed by clinical findings. A key difference between cellulitis and other erythematous skin lesions is its unifocality. Cellulitis rarely presents bilaterally or in a disseminated distribution unless in an immunocompromised host (Reference 12). Blood cultures do not aid in diagnosis because they are positive less than 5% of the time. Invasive diagnostic procedures such as needle aspiration and skin biopsies are seldom performed because of their variable yield; however, they may be useful when it is necessary to identify the causative organism in patients with underlying comorbidities (References 13, 14).

Treatment

Initial treatment of erysipelas should include oral antibiotics with streptococcal coverage. Most GAS remains susceptible to β-lactams (including penicillins and cephalosporins). In patients with severe penicillin allergies, clindamycin and macrolides are reasonable alternatives, assuming that local resistance rates are low (Reference 15). Patients presenting with systemic symptoms should be treated aggressively with parenteral antibiotics, followed by oral antibiotics once fever subsides and the cutaneous progression of the infection is halted. A 10- to 14-day treatment course is typically recommended.

Empiric antibiotic regimens for uncomplicated, nonpurulent cellulitis should cover GAS and MSSA. Because most patients can be treated with oral antibiotics, appropriate medications may include cephalexin, dicloxacillin, clindamycin, or macrolides. Patients presenting with suppurative cellulitis should receive oral antibiotics against CA-MRSA such as TMP/SMX, clindamycin (if local resistance rates are less than 10%), or a tetracycline, pending culture results.

In hospitalized patients with suspected cellulitis, parenteral options include a penicillinase-resistant penicillin (e.g., oxacillin, nafcillin), a first-generation cephalosporin (e.g., cefazolin), a combination β-lactam/β-lactamase inhibitor (e.g., ampicillin/sulbactam), clindamycin, or vancomycin (Reference 3). The IDSA practice guidelines recommend broadening the scope of antibiotics to cover CA-MRSA in patients with complicated SSTIs (e.g., deep soft tissue infections, surgical/traumatic wound infection, major abscesses, infected ulcers, and burns), those who do not respond to initial therapy, or those who

present with systemic toxicity. In addition to surgical debridement, antibiotic options specific to pediatrics include vancomycin (with a targeted trough of 10–15 mg/dL), clindamycin, and linezolid (Reference 7).

Treatment duration in uncomplicated cellulitis is typically 5–10 days. Longer therapy durations may be necessary for complicated cases and should be individualized on the basis of patient response. Elevation of the infected area promotes gravity drainage of edema and inflammatory substances. Underlying conditions that may predispose a patient to secondary cellulitis (e.g., immunosuppression, trauma, primary skin conditions such as eczema) should also be addressed.

Impetigo

Impetigo is an infection of the superficial dermis that results in purulent lesions. The infected vesicle can easily rupture, causing the contents to form a honey-colored crust. Primary impetigo can be further classified as non-bullous or bullous. Non-bullous impetigo (also known as impetigo contagiosa [IC]) is characterized by the aforementioned crusted appearance. Bullous impetigo (BI), by contrast, is characterized by friable, fluid-filled vesicles or blisters (Reference 16).

Impetigo is the third most common type of skin infection in children, typically affecting children 2–5 years of age (Reference 17). Seventy percent of all impetigo cases are non-bullous because of the high contagiousness of impetigo (Reference 18). Transmission occurs through direct contact; thus, conditions of crowding and poor hygiene, day care, and warm climates are risk factors for outbreaks. Predisposition to disease depends on host factors such as atopy, immunosuppression, renal impairment, and diabetes (Reference 16). Bullous impetigo occurs more commonly in children younger than 5 years; however, most cases are diagnosed in neonates, possibly because of their lack of immunity against and impaired clearance of staphylococcal toxins (Reference 16).

Microbiologic Etiology

The most common causative organisms for IC are *S. aureus,* GAS, or a combination of the two (Reference 18). Bullous impetigo is almost exclusively caused by *S. aureus* (Reference 19). The incidence of MRSA in impetigo was less than 20% in a Japanese study conducted between 1994 and 2000, but its frequency is increasing (References 3, 19).

Colonization with *Streptococcus* or *Staphylococcus* is believed to precede the development of active impetigo (Reference 3). Exfoliative exotoxins produced by *S. aureus* are virulence factors in both forms of impetigo, but especially in BI. The same exotoxins are implicated in staphylococcal scalded skin syndrome (SSSS), which is thought to be a more systemic version of BI (Reference 16).

Clinical Presentation

In IC, lesions usually begin as small red macules that quickly turn into vesicles surrounded by erythema. The vesicles become pustular and rupture to give a thick honey-colored crust. Satellite lesions may appear when autoinoculation, or host reinfection, occurs at open breaks in the skin. Pruritus and other systemic complications, such as peripheral erythema and local lymphadenopathy, may be present. Areas commonly affected include the face and extremities.

Most impetigo cases are self-limiting and resolve without scarring within weeks. However, acute poststreptococcal glomerulonephritis may affect 1% to 5% of patients with IC (Reference 20). This risk is not attenuated by appropriate antibiotic treatment. Complications of systemic staphylococcal disease include SSSS, sepsis, cellulitis, pneumonia, lymphangitis, and osteomyelitis (Reference 19).

Bullous impetigo typically evolves from rapidly enlarging vesicles to flaccid bullae over normal skin with limited erythema. The encased fluid turns turbid and often ruptures within 48 hours, resulting in thin brown to golden-yellow crusts. The formation of collarette scales in the periphery of a ruptured lesion is a pathognomonic finding of BI (Reference 21) (Figure 3). Trunks and extremities are commonly affected, as are areas around the nose, mouth, and moist intertriginous zones, such as the diaper area, neck folds, and axillae. Systemic complications are uncommon.

Diagnosis

Diagnosis is often made on clinical appearance alone. Microbiologic analysis and skin biopsies are rarely indicated, except to clarify cases of extensive involvement or in patients who do not respond to initial antibiotics.

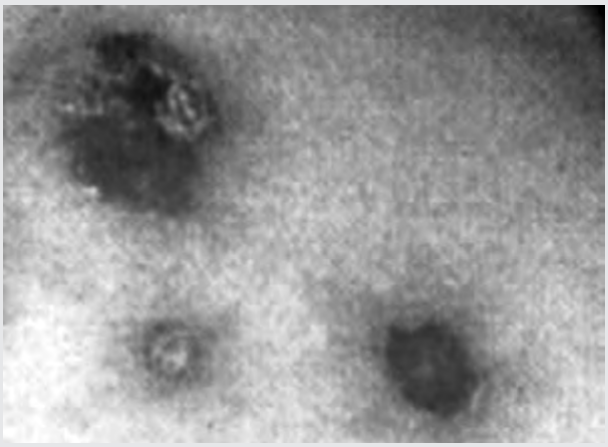


Figure 3. Bullous impetigo with circumscribed lesions and thin collarettes of scales. Images reprinted with permission from Medscape.com, 2011.

Bacteria may be cultured from the blister contents. Antistreptococcal antibody assays do not aid in diagnosing IC but provide supporting evidence of recent systemic streptococcal infection in patients with suspected post streptococcal glomerulonephritis.

Treatment

Expert opinions recommend a 7-day course of topical treatment for localized, uncomplicated impetigo cases (References 3, 16). The basis of this recommendation is derived from meta-analyses examining the comparative efficacy of various outpatient regimens (References 22, 23). Topical antibiotics, such as mupirocin 2%, fusidic acid 2% (not available in the United States), and gentamicin 0.1%, were clinically superior compared with placebo (Reference 22). Among the topical antibiotics, comparisons of mupirocin and fusidic acid did not show a difference in clinical outcome (Reference 22).

In more recent literature, protein synthesis inhibitors called pleuromutilins have shown good in vitro activity against various streptococcal and staphylococcal species (Reference 24). Retapamulin is the first topical agent in this category licensed for impetigo caused by MSSA or *S. pyogenes* in patients 9 months or older (Reference 25). When applied twice daily for 5 days, retapamulin 1% ointment was found superior to placebo for the treatment of impetigo and non-inferior to fusidic acid (References 26, 27). Although clinical studies have suggested its efficacy against a few fusidic acid and mupirocin-resistant strains, this has not been shown on a large scale (Reference 27).

In two meta-analyses, topical treatment was favored over oral antibiotics for uncomplicated impetigo (References 22, 23). However, robust studies comparing topical and oral treatments remain deficient. In general, oral antibiotics should be reserved for cases of recalcitrant, extensive, or systemic disease. Because of the predominance of *S. aureus* in BI and IC, penicillinase-resistant penicillins, β-lactam/β-lactamase combinations, or first-generation cephalosporins are appropriate first-line oral antibiotic choices for the treatment of extensive impetigo. Macrolides may be substituted in patients with true penicillin allergies but only in regions with less than 10% macrolide resistance or confirmed macrolide susceptibility. When MRSA is suspected, clindamycin or TMP/SMX should be considered. Because no clinical trials have shown the superiority of one antibiotic over another, choice of an optimal regimen will depend on local susceptibility data and patient-specific factors, such as contraindications, allergies, and tolerance of adverse effects. Recommended length of therapy is 7 days (References 16, 19).

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome, an infection caused by certain strains of *S. aureus*, results in the loss of keratinocyte cell adhesion and leads to blistering of the upper layer of the skin. These flaccid bullae rupture easily to reveal an erythematous base, giving rise to a moist, scalded appearance and widespread desquamation (Reference 28). Staphylococcal scalded skin syndrome is believed to be a generalized form of BI because of their shared virulence factor, the exfoliative toxin (ET), which compromises intercellular adhesion and gives rise to the pathognomonic histologic findings of mid-epidermal separation at the zona granulosa (Reference 29).

Staphylococcal scalded skin syndrome usually presents in children younger than 5 years. Disease transmission is likely through contact with asymptomatic carriers of *S. aureus*. Infants and young children may be especially susceptible because of waning immunity from maternal antibodies and impaired renal clearance of ET (Reference 29). Mortality in childhood SSSS is 5% but may exceed 60% in adults (Reference 30).

Microbiologic Etiology

Staphylococcal scalded skin syndrome, by definition, is caused by *S. aureus*–bearing ET-encoding genes, which were detected in up to 10% of all *S. aureus* strains in a recent study from Europe (Reference 31). A greater percentage of MRSA strains express these genes than do MSSA strains, though the clinical significance of this is unknown. Currently, there are very few cases of MRSA causing SSSS reported in the literature (References 32–34). Most SSSS cases in the United States are caused by *S. aureus* phage type II, which is predominantly methicillin sensitive (References 29, 35).

Clinical Presentation

Patients may present with a prodrome of sore throat and conjunctivitis, accompanied by constitutional symptoms of fever, malaise, and irritability. Within 48 hours, exquisitely tender erythematous patches, which rapidly erupt on the face, neck, axilla, and perineum, may develop into non-tense bullae that rupture to reveal a friable, erythematous base susceptible to denuding by simple rubbing (e.g., positive Nikolsky sign) (Figure 4). Large areas of the skin may be involved, particularly in flexural and perioral regions. Mucous membranes are spared (Figure 5). Complications include secondary infections, electrolyte disturbances, and difficulties in temperature regulation (References 29, 30, 36, 37).



Figure 4. Erythematous patches on the torso, arm, and neck characteristic of staphylococcal scalded skin syndrome. Photo credit: Dr. James Corb, Children's Hospital of Orange County.



Figure 5. Perioral peeling from staphylococcal scalded skin syndrome. Photo credit: Dr. James Corb, Children's Hospital of Orange County.

Diagnosis

Generalized SSSS is a manifestation of the hematogenous spread of ET produced by bacteria from a focus of colonization (nares, eye, umbilicus, groin, or wound site) or active infection (pneumonia, osteomyelitis, or endocarditis). The yield of bacterial cultures from blister aspirates and blood is generally poor because symptoms are mediated through toxins released by organisms residing in extracutaneous reservoirs. However, isolation of *S. aureus* from a suspected focus of infection may be confirmatory (References 36, 37).

Treatment

Although limited evidence exists to guide the optimal treatment of SSSS, a parenteral antibiotic with staphylococcal activity (i.e., penicillinase-resistant penicillin or a first- or second-generation cephalosporin) is recommended and should be initiated promptly. The addition of clindamycin as an adjunct to any regimen should be strongly considered because of its ability to attenuate toxin production (Reference 37). Because patients with extensive exfoliation are at high risk of secondary gram-negative infections or septicemia, some experts recommend adding gentamicin to an antistaphylococcal regimen or changing to a third-generation cephalosporin plus clindamycin (References 16, 29). Lack of symptomatic improvement within 48 hours should also prompt expanded coverage to include MRSA.

Eroded areas are best covered with bland emollients, such as petrolatum, to prevent moisture loss and protect against bacterial infections. Topical antibiotic ointments may be prescribed for conjunctivitis and mupirocin for nasal decolonization. Extensive skin involvement may necessitate additional treatment considerations, including aggressive pain management, fluid and nutritional support, temperature regulation, and prevention of pressure sores and secondary infections. In outbreaks, carriers should be immediately identified and treated with antistaphylococcal antibiotics.

Exfoliation may continue for 24–48 hours after the initiation of appropriate antibiotic therapy until toxin production ceases. Thereafter, skin lesions should heal rapidly in 7–10 days with minimal scarring because only the superficial layers are affected (Reference 29). Typical length of antibiotic treatment is at least 10 days.

Cutaneous Abscesses

A cutaneous abscess is an encapsulated collection of pus within the dermis and deep skin tissues that is accompanied by swelling and an erythematous rim. It is among the leading causes of pediatric outpatient clinic visits. In an epidemiologic study of SSTIs in the United States between 2001 and 2003, pediatric patients represented 24% of an estimated 11.6 million SSTI-related visits in

an ambulatory care setting (Reference 38). The combined category of cutaneous abscesses and cellulitis accounted for 62% of all SSTI diagnoses and rose 15% in incidence compared with statistics from 1992 to 1994 (Reference 38). The disease burden also appeared to shift from the physician's office to the outpatient clinic and emergency department because the visit rates for the latter two settings increased by 59% and 31%, respectively, during these periods (Reference 38). The authors surmised that these trends, in part, coincided with the emergence of CA-MRSA as a pathogen during the late 1990s, which is associated with a rapidly progressive onset that would cause patients to seek treatment in urgent care settings.

In recent years, SSTIs (particularly abscesses) have continued to be the most common manifestation of CA-MRSA (Reference 4). Although nasal colonization with MRSA has been identified as a risk factor for recurring SSTIs, its predictive value for new infections within a community is not fully understood (Reference 39). Because MRSA can also reside in other sites including the pharynx, axillae, rectum, and perineum, one pediatric study suggests a stronger correlation between rectal MRSA colonization and abscess development than nasal MRSA colonization (Reference 40).

Microbiologic Etiology

S. aureus is the most common bacteria isolated from cutaneous abscesses, accounting for 66% to 82% of all samples obtained through incision and drainage (I&D) in four recent pediatric studies (References 40–43). Of note, the incidence of CA-MRSA has increased significantly, now representing 49% to 100% of *S. aureus* cultures isolated from abscesses in pediatric patients (References 40–44). One study observed an increase in the incidence of MRSA by 80% between 2003 and 2006 (Reference 43).

Although most abscesses occurring above the trunk and extremities are caused by *S. aureus*, anaerobic organisms such as *Peptococcus* spp. and *Propionibacterium* spp. may also be involved. Abscesses in the perineal region are often polymicrobial, containing anaerobic and aerobic bacteria that constitute the normal flora of regional skin and mucous membranes (Reference 2).

Clinical Presentation

Abscesses typically result from minor trauma to an area that becomes infected. The area may develop a nodule, which can become fluctuant or pustular and is surrounded by erythematous swelling (Figure 6). It is usually painful and tender. Accompanying features can include local cellulitis, lymphangitis, regional lymphadenopathy, fever, and leukocytosis (Reference 2).

One prospective study noted that most abscesses in children developed around the diaper area, namely the gluteus (43%), perineum/labia (5.4%), and inguinal (7.4%) areas; other locations included the upper leg (8.1%), lower leg (8.4%), axilla (13.4%), forearm (2.7%), abdomen (8.1%), and head (3.3%) (Reference 44).

Diagnosis

The diagnosis of cutaneous abscesses should not be based on clinical examination alone because agreement among evaluators can be poor (Reference 45). Assessment methods that are more objective, such as bedside ultrasonography, can help determine the presence of a drainable fluid collection (Reference 46). Gram staining and culture may be especially useful in the presence of several lesions, surrounding cellulitis, systemic manifestations of infection, or an immunocompromised host (Reference 3).

Treatment

Incision and drainage is the cornerstone of therapy for the treatment of cutaneous abscesses (Reference 7). There is a paucity of controlled comparative trials to guide the treatment of this disease state. A recent randomized, double-blind study comparing placebo with 10 days of TMP/SMX after I&D of skin abscesses in 149 children showed that both groups experienced similarly low rates of treatment failure when evaluated at 10 days (Reference 47). This finding was also true in the subset of patients infected with CA-MRSA who did not see a greater rate of clinical resolution while receiving appropriate antibiotics. Although the use of inappropriate antibiotics may not be associated with worse outcomes, an infected area greater than 5 cm in diameter may be (Reference 48).

The IDSA practice guidelines do not advocate continuing antibiotics after I&D for simple abscesses (Reference 7). However, antibiotic therapy should be



Figure 6. An erythematous, fluctuant abscess in the axilla. Photo credit: Dr. James Corb, Children's Hospital of Orange County.

considered in complicated disease or specific hosts (Table 1). If antibiotics are initiated, empiric coverage for CA-MRSA is recommended until culture and sensitivity results are known. Initial oral options may include TMP/SMX, clindamycin, and doxycycline. Linezolid, given its wide spectrum of activity against other drug-resistant organisms and comparatively expensive cost, should be reserved as a last resort for outpatient management. In hospitalized children, vancomycin is recommended with a trough goal of 10–15 mg/dL. Parenteral clindamycin and linezolid are other options if the patient is stable without ongoing bacteremia or intravascular infection (Reference 7).

Table 1. Patients for Whom Antibiotic Therapy Is Recommended After I&D of Simple Abscess (Reference 7)

- Severe or extensive disease (e.g., involving many infection sites)
- Rapid progression in the presence of associated cellulitis, signs and symptoms of systemic illness
- Associated comorbidities or immunosuppression (diabetes mellitus, human immunodeficiency virus infection/AIDS, neoplasm)
- Extremes of age
- Abscess in area difficult to drain
- Associated septic phlebitis
- Lack of response to I&D alone

AIDS = acquired immunodeficiency syndrome; I&D = incision and drainage.
Information from Liu C, Bayer A, Cosgrove S, Daum R, Fridkin S, Gorwitz R, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:1–38.

Animal and Human Bites

Animal and human bites are wounds that can result in infectious complications. The incidence of animal bites in the United States is estimated to be 2–5 million per year, with most cases occurring in children. Around 85% to 90% of bite injuries are caused by dogs, followed by cats (5% to 10%) and humans (2% to 3%) (Reference 49). About 1.3 in 1000 people with dog bites require medical treatment, with the highest incidence being among 5- to 9-year-old boys (6 in 1000 people) (Reference 50). There is much less epidemiologic information on cat bites specific to children. In one prospective study of patients presenting to the emergency department with cat bites, 58% of patients were younger than 21 years, among which the greatest portion were patients younger than 6 years (Reference 51). Human bites have been characterized by some as a "leisure time injury of the young single male" on the basis of an epidemiologic study showing a predominance of males between 16 and 20 years of age and a possible association with alcohol use (Reference 52). In this same study, children younger than 15 years accounted for 12% of human bite injuries presenting at an emergency department (Reference 52). Around 1% to 3% of human bites in children are from child abuse (Reference 49).

Microbiologic Etiology

Sources of bacteria recovered from a bite wound are those that colonize the victim's skin and those that derive from the oral cavity of the aggressor, as well as environmental organisms. In one study involving children who sustained injuries from animal bites (17 dogs, 4 cats), an average of 2.8 organisms were isolated from each specimen, more than 66% of which were a combination of aerobic and anaerobic bacteria (Reference 53). In an adult study that analyzed the bacteriology of wounds associated with clinical signs of infection, *Pasteurella* spp. was the most frequent isolate, followed by *Streptococcus* spp., *Staphylococcus* spp., *Moraxella* spp., and *Neisseria* spp. Anaerobes included *Fusobacterium* spp., *Bacteroides* spp., *Porphyromonas* spp., and *Prevotella* spp. (Reference 54). Dogs and cats, as well as other feral animals, may be carriers of rabies. *Bartonella henselae*, which is associated with a febrile illness known as "cat scratch disease," is a pathogen unique to cat bites. Common aerobic microbes isolated from human bite injuries include *Streptococcus anginosis*, *S. aureus*, coagulase-negative *Staphylococcus*, *Enterococcus* spp., *Corynebacterium* spp., and *Eikenella corrodens*. *Prevotella* spp., *Porphyromonas* spp., *Bacteroides* spp., *Fusobacterium* spp., and *Peptostreptococcus* spp. are typical anaerobic pathogens (Reference 55). Moreover, hepatitis B and C, as well as human immunodeficiency virus (HIV), can rarely be transmitted from the aggressor to the victim through bite injuries (Reference 56).

Clinical Presentation

Anatomic differences in the tooth shapes of cats and dogs result in wound profiles unique to each animal. Cat teeth are long and slender, which are more likely to inflict small but deep puncture wounds. Most cat bites do not penetrate beyond the dermis; however, in one study, 25% of wounds damaged the subcutaneous layer, and 4% affected muscle, tendon, or bone (Reference 51). In contrast, dog bites are predominantly crush injuries, lacerations, or abrasions that result in partial skin penetration (Reference 57). In children, the hands and arms are the most common wound sites for cat bites,

compared with head and neck injuries with dog bites (References 51, 58). Around 4% of wounds associated with dog and cat bites result in hospitalization (References 50, 51). Human bites are typically located on the face, upper extremity, or trunk and can range in presentation depending on the mechanism of injury. Two types of bite wounds are common: (1) an occlusional injury, which is a direct penetration trauma to the skin tissue caused by the biter's teeth, and (2) a clenched-fist injury, in which bacteria inoculated through the broken skin of a fist in a flexed position travel caudally to tendons and joints when the hand is relaxed to cause deeper infections. Because the intercanine distance of an adult is typically 2.5–4 cm, the presentation of a lesion with said dimensions on a child may be suggestive of abuse (Reference 49).

It is estimated that 3% to 18% of dog bites and 28% to 80% of cat bites become infected (Reference 54). Patients presenting 12 hours after the inciting event likely have established infection (Reference 3). The wound site may appear edematous, erythematous, and bruised, and it may drain serosanguineous fluid. Pain is a common finding. Lymphadenopathy, streaking, and fever can signify more systemic complications such as cellulitis, subcutaneous abscesses, osteomyelitis, tendonitis, and, rarely, bacteremia (Reference 3).

Several studies have sought to identify risk factors correlated with the development of wound infections. For cat bites, these included deep puncture or full-thickness wounds and injuries to the extremities. Of interest, facial wounds had lower absolute risks of infection, perhaps because of the increased blood supply to the area (Reference 51). The three strongest predictors of infection after a dog bite are wound depth, need for wound debridement, and female sex, though factors such as wound location or type and time between wound and debridement have been identified as secondary determinants (References 57, 59). Human bites can result in infection in 10% to 15% of cases (Reference 60). Clenched fist injuries are particularly prone to complications because relaxation of the hand brings the wound closer to tendons, metacarpal heads, and joint spaces, where the infection can spread.

Diagnosis

Diagnosis is based on a positive history of interaction with an animal or individual who inflicted the wound, as well as a clinical examination. Cultures should only be obtained for wounds more than 8–12 hours old or those that appear infected. Radiography is indicated if there is concern about injury to deep structures or a need to assess foreign body inoculation (References 61, 62).

Treatment

The goals of bite wound management are the treatment or prevention of infection and minimization of soft tissue damage. Many treatment algorithms, which are largely based on expert opinion, focus on timely wound cleaning, irrigation, debridement, and closure if appropriate. The wound should be cleansed with clean water and gentle soap to remove any visible dirt. Soaking the injury or using alcohol or peroxide is not recommended because of the potential for further tissue injury. Irrigation with a saline lavage can be administered with a 30-mL syringe and 18-gauge intravenous catheter. Debridement is indicated for the removal of any foreign body or devitalized tissue. Edematous wounds should be passively elevated to encourage lymphatic drainage and accelerate healing. The decision on whether to close a wound is controversial. Fresh, non-punctured wounds that are limited and thoroughly cleaned may be closed by primary intention. Surgical closure of bite wounds to the neck and face up to 24 hours after the injury, together with the administration of prophylactic antibiotics, is a reasonable treatment strategy because of good vascular supply to the area and cosmetic considerations (Reference 49). All wounds with established infection or at high risk of infection, including puncture wounds, crush injuries, wounds more than 12–24 hours old, hand or foot wounds, cat or human bites, or wounds in immunocompromised individuals, should not be sutured but kept well bandaged (References 49, 56). Immunoprophylaxis against tetanus, rabies, hepatitis, and HIV should be considered after a human bite on the basis of the aggressor's clinical history and the patient's immune status. The reader is referred to the Centers for Disease Control and Prevention Web site for current guidelines on postexposure prophylaxis for the aforementioned diseases.

Most uncomplicated bite injuries can be managed in the outpatient setting. Prophylactic antibiotics in low-risk wounds (early presenting, non-infected, non-puncturing) have limited benefit and are not routinely recommended (Reference 63). However, a 3- to 5-day oral course should be considered in selected cases (Table 2) (References 3, 49, 53, 56). Close follow-up is indicated in the next 48 hours to monitor for signs of developing infection.

Patients presenting with signs of established infection after an animal bite should be empirically treated with antibiotics, which will cover the typical pathogens including *S. aureus, Pasteurella multocida,* and other anaerobes. Empiric coverage for human bites should cover mixed flora, with special attention to *E. corrodens*, because it is not susceptible to first-generation cephalosporins. Outpatient management with oral amoxicillin/clavulanate is first line for all mammalian bites, with TMP/SMX or an extended-spectrum cephalosporin

Table 2. Indications for Prophylactic Antibiotics After a Mammalian Bite (References 3, 49, 56)

- Human bite wounds
- Puncture wounds beyond the epidermis
- Wounds with associated crush injury and edema
- Wounds on the hands/feet or in proximity to a bone or joint
- Facial bites
- Genital area bites
- Wounds present in complicated hosts (extremes of age, immunocompromised or asplenic, chronic disease)

Information from Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. Clin Infect Dis 2005;41:1373–406; Kannikeswaran N, Kamat D. Mammalian bites. Clin Pediatr 2009;48:145–8; Thomas N, Brook I. Animal bite-associated infections: microbiology and treatment. Expert Rev Anti Infect Ther 2011;9:215–26.

(e.g., cefuroxime) in combination with clindamycin as alternatives in patients with penicillin allergies (References 56, 62). Other oral alternatives include doxycycline and the fluoroquinolones, which when dictated by cultures and sensitivities, may be used safely in children. Intravenous antimicrobials with activity against mixed flora such as β-lactam/β-lactamase inhibitor combinations, TMP/SMX plus clindamycin, and second-generation cephalosporins with anaerobic activity (e.g., cefoxitin) are suitable empiric choices for severe infections (References 56, 62). Broad-spectrum carbapenems should be reserved for treatment failure or drug-resistant isolates. Therapy duration will vary by the severity of injury, but it can range from 7–14 days for soft tissue infections to 3–6 weeks for involvement of the joints or bones (References 3, 56, 62).

Deep Bacterial Tissue Infections

Periorbital and Orbital Cellulitis

The orbital septum is a fibrous tissue that arises from the periosteum of the skull and continues into the eyelids. This anatomic landmark serves as a barrier to prevent superficial infections from penetrating deep into the orbit. Infections occurring in the soft tissue anterior to the septum are called periorbital cellulitis (PC), whereas those occurring posterior to the septum are considered orbital cellulitis (OC). Periorbital cellulitis is a disease that occurs in young children, particularly those younger than 5 years. Males and females are equally affected. In comparison, OC is only one-third as common as PC and tends to affect children 5-7 years of age (References 64–70). Epidemiologic studies of OC describe a 2:1 male predominance (References 66, 68, 70, 71). Because of its association with upper respiratory tract infections, OC tends to occur more frequently in the winter (References 66, 71).

Predisposing factors for orbital infections include upper respiratory tract or sinus infections, extension of external ocular infections, dental abscesses, superficial breaks in the skin from underlying skin conditions, an insect bite, a penetrating injury to the orbit, periocular surgery, and hematogenous seeding (Reference 71).

Microbiologic Etiology

The organisms responsible for PC and OC have historically been the same bacteria implicated in respiratory tract and sinus infections; however, widespread administration of childhood Haemophilus and streptococcal vaccines may shift the types of causative pathogens.

Periorbital cellulitis seeded from minor trauma to the skin is often caused by staphylococcal and streptococcal species, which account for greater than 70% of positive cultures (e.g., orbital/sinus, conjunctiva, blood) obtained from infected children (References 66–69, 71). Orbital cellulitis is often a complication of acute sinusitis (specifically the ethmoid sinus); thus, respiratory organisms such as *Streptococcus pneumoniae*, GAS, other streptococcal species (*S. anginosus*), *S. aureus*, nontypeable *H. influenzae,* or *Moraxella catarrhalis* are common pathogens. Although *S. aureus* is often implicated in these disease states, the pervasiveness of MRSA appears to be highly regional, ranging from 13% to 73% (References 65, 70). Mixed or polymicrobial infections, sometimes involving anaerobic organisms, tend to occur more commonly in older children because of the greater constriction between the sinus and their drainage passages, which impedes aeration and leads to an overgrowth of microbial flora (Reference 64).

Clinical Presentation

Both PC and OC can present with unilateral ocular erythema, edema, warmth, and tenderness (Figure 7). Fever and other systemic signs may also be seen. Other symptoms specific to OC, related to its invasiveness and potential to increase intraorbital pressure, include chemosis, blurred vision, impaired ocular movements, and proptosis (Figure 8). In general, markers for an inflammatory response are more robust in OC, manifested as higher fevers, greater elevation of C-reactive protein, and a more dramatic left shift (Reference 71).

Most patients recover from PC and OC without any long-term sequelae. Complications from PC include local abscess formation, development of OC, and intracranial extension of infection. Untreated OC can



Figure 7. Periorbital and orbital cellulitis can both present with fever, acute unilateral eyelid erythema, and limited extraocular motions. Photo credit: Dr. Thomas F. Sellers, Centers for Disease Control and Prevention.



Figure 8. Orbital cellulitis with proptosis, ophthalmoplegia, and edema and erythema of the eyelids. Images reprinted with permission from Medscape.com, 2011.

lead to significant morbidity from vision loss; intracranial infections such as meningitis, subdural empyemas, and abscesses; and cavernous sinus thrombosis (Reference 71).

Diagnosis

Periorbital cellulitis and OC are diagnosed largely by physical examination. The use of computed tomography (CT) in differentiating between PC and OC is controversial because definitive diagnosis and staging are difficult. However, CT may be indicated when patients exhibit central nervous system involvement or deterioration in visual acuity (Reference 71). Positive radiographic evidence of sinusitis in the ethmoid and maxillary cavities, as well as subperiosteal or orbital abscesses and diffuse fat infiltration, is seen more often in cases of OC than PC.

Microbiologic confirmation of orbital infections is best obtained by surgical sampling, whereby yields in excess of 80% are reported (References 65, 70). Less invasive swabs obtained from the conjunctiva and sinus aperture also are more likely to be positive than blood cultures, which are usually of low yield (less than 7%) (References 64–66, 69, 70).

Treatment

Literature regarding the management of PC and OC is largely retrospective and based on expert opinion. Simple PC without systemic involvement may be treated with empiric oral antibiotics that cover pathogens associated with the likely cause of infection. Local prevalence of MRSA should be considered when determining *S. aureus* coverage. A treatment course of 7–10 days is generally sufficient (Reference 71).

No clear consensus exists on which patients should be hospitalized for parenteral antibiotics, but some experts consider children high risk if they have suspected PC exhibiting signs of systemic illness, or any suspected cases of OC, especially in children younger than 12 months (Reference 69). Empiric parenteral antibiotics should cover *Streptococcus* spp., common respiratory pathogens, *S. aureus* (including MRSA when appropriate), and anaerobes. A β-lactam/β-lactamase inhibitor combination is a reasonable initial choice. If sinus involvement with respiratory pathogens is suspected, a second- or third-generation cephalosporin plus clindamycin can be tried. Vancomycin may be substituted for clindamycin for enhanced MRSA coverage; however, anaerobic coverage may need to be bolstered with metronidazole. Parenteral antibiotics should be narrowed on the basis of susceptibility data and continued until systemic symptoms have resolved and significant improvement is seen in the eye, at which point an oral agent may be substituted to complete a 10- to

14-day course. Medical management alone may be adequate for treating OC, especially in children younger than 9 years or those presenting with no or only small subperiosteal abscesses (References 69, 72). Evaluation for surgical intervention is indicated in patients with significant visual impairment; frontal sinus or pansinusitis; defined abscesses; prominent mass effect; gas in the orbit; ophthalmoplegia; or lack of clinical improvement despite adequate parenteral therapy (References 69, 73).

Necrotizing Fasciitis

Necrotizing fasciitis is a potentially life-threatening infection of the subcutaneous tissues comprising the superficial fascial plane, characterized by rapid and widespread inflammation and necrosis. The incidence of NF in adults has been reported to be 0.40 cases per 100,000, and the incidence in children is 0.08 cases per 100,000 (References 74, 75). Infections can be polymicrobial or monomicrobial, with most of the latter caused by GAS. In a prospective surveillance study of all Canadian children younger than 16 years, non-GAS-related NF and GAS-related NF accounted for 0.81 and 2.12 cases per 1 million children, respectively (Reference 76). Most children were younger than 5 years (Reference 76).

General risk factors for NF include conditions that compromise skin integrity, such as recent trauma or skin lesions. Non-GAS-related NF is associated with chronic illnesses, malnutrition, obesity, immunosuppression, and intravenous drug use. In neonates, non-GAS-related NF can develop secondary to surgery, procedures, or necrotizing enterocolitis (Reference 77).

In contrast, GAS-related NF generally affects healthy children. A strong correlation has been noted between GAS-related NF and varicella infection. Fifty-eight percent of patients from the Canadian study were recently given a diagnosis of varicella (Reference 76). Although an association between nonsteroidal anti-inflammatory drugs (NSAIDs) and GAS-related NF has been reported in many case reports, a causal relationship has not been proved (Reference 78).

Microbial Etiology

Group A β-hemolytic *Streptococcus* is the most common cause of monomicrobial NF, though other bacteria have been implicated, such as *S. aureus, Vibrio vulnificus, Aeromonas hydrophila,* and *Peptostreptococcus* spp. Invasive GAS infections can occur from the translocation of colonized GAS in the pharynx through systemic spread to the site of minor trauma; however, more often than not, the infection occurs spontaneously with no preceding prodrome. The pathogenesis of GAS is facilitated by several important cell surface proteins that help it evade phagocytosis: proteases, which can precipitate intravascular occlusion; and pyrogenic exotoxins, which can act as superantigens (Reference 79).

In contrast, polymicrobial NF is a mixed infection involving anaerobic bacteria, such as *Bacteroides* and *Peptostreptococcus* spp., and bowel flora, including coliforms and anaerobic bacteria (Reference 3). Critically ill neonates are especially vulnerable to polymicrobial NF involving *S. aureus* because of the variety of monitoring and surgical procedures they undergo (Reference 77).

Clinical Presentation

Patients with early stages of NF present with mild swelling and erythema over an affected site, but they may report pain seemingly out of proportion to the infection. High temperatures, tachycardia, altered mental status, and systemic toxicity are common. In children and neonates, the most common infection sites are the trunk, followed by the head and neck, limbs, lower extremities, and perineum (References 76, 77, 80). Eventually, necrosis of the soft tissue, skin ischemia, and gangrene of the overlying skin ensue and can give rise to blister or bulla formation and skin ulceration. Damage to superficial nerves can lead to the loss of sensation. Rapidly advancing erythema without margins, lack of response to appropriate antibiotics, and progression to systemic signs of sepsis should suggest NF. Symptoms generally progress for 2–4 days, but GAS-related NF tends to spread very quickly and can culminate in multisystem organ failure early in the disease process (References 74, 81). In two pediatric case series, complications occurred in 78% to 85% of patients, and mortality ranged from 5.4% to 18% (References 76, 82). Immunocompromised status was an independent risk factor for mortality (References 82, 83).

Diagnosis

Laboratory evaluation of patients with suspected NF is nonspecific but reflects evidence of systemic inflammation and organ dysfunction. One adult study found that a composite scoring system based on elevations in C-reactive protein, white blood cell count, hemoglobin, serum sodium, creatinine, and glucose was correlated with an increased likelihood of NF (Reference 84). This has not been validated prospectively in children.

Evidence of NF on ultrasonography may include the presence of fluid accumulation within thickened fascia or loculated abscesses. Gas in the soft tissue is a positive finding by plain radiography in 24% to 73% of patients, especially in patients with non-GAS-related NF (Reference 81). Magnetic resonance imaging and CT can be useful in distinguishing cellulitis from necrotizing infections.

Samples from the blood and surgically obtained deep tissue should be cultured to identify the pathogen and tailor antibiotic treatment. For rapid microbiologic evaluation, Gram staining can be performed on any discharge from the wound, blisters, or histologic samples. Frozen section biopsy can provide confirmation of the diagnosis (Reference 3).

Treatment

Surgical management is the first line of treatment in NF. Aggressive debridement of the wound up to the first margins of pink, viable tissues is required to control disease morbidity because NF can invade areas beyond the extent of visibly involved skin. Often, multiple, sequential debridement is necessary until signs of disease progression have stopped. Occasionally, amputation may be necessary. Meticulous wound management after surgery is critical, given the often extensive area involved and risk of secondary infections.

Empiric antibiotics should be continued until debridement is no longer needed, clinical improvement has been seen, and fever has subsided for at least 72 hours. If GAS is suspected, the combination of clindamycin and penicillin has shown superior clinical efficacy to penicillins alone (Reference 85). Pharmacologically, clindamycin may suppress toxin production, modulate cytokine production, and sustain bacterial killing during slow phases of growth when penicillins are ineffective. Empiric coverage for polymicrobial infections should include agents with an expanded spectrum of activities against gram-negative organisms and anaerobes. Regimens recommended by the IDSA include a β-lactam/β-lactamase combination and clindamycin plus ciprofloxacin, a combination of metronidazole or clindamycin with a third-generation cephalosporin, or monotherapy with a penicillin/penicillinase combination or carbapenem (Reference 3). Although the IDSA makes no recommendations specific to the treatment of NF in children, the combination of clindamycin and a third-generation cephalosporin or monotherapy with a β-lactam/β-lactamase combination are reasonable empiric regimens that would cover both monomicrobial and polymicrobial NF (Reference 15). Additional gram-negative and anaerobic coverage may be required in children at risk of polymicrobial NF because of underlying medical conditions and immunocompromised states. When antimicrobial options are limited because of pathogen susceptibility and need for tissue penetration, the benefit of fluoroquinolone use in children is believed to outweigh the minimal risks of musculoskeletal adverse effects, which is endorsed by the American Academy of Pediatrics (AAP) (Reference 86).

Given the suggested role of superantigens in the pathogenesis of GAS-related NF, intravenous immunoglobulin (IVIG) may help attenuate the untoward host inflammatory effect by neutralizing superantigens. Despite in vitro data and smaller case series that suggest benefit, this has not been reproduced in larger-scale studies (Reference 87). In the only multicenter, placebo-controlled trial of adults with streptococcal toxic shock syndrome, adjunctive therapy with IVIG showed a trend toward benefit (Reference 88); however, a recent retrospective review of IVIG use in children with streptococcal toxic shock syndrome showed no difference in clinical outcomes compared with patients who did not receive IVIG (Reference 89). The routine use of IVIG remains controversial in the absence of substantial clinical benefits, high cost, and scarcity. Intravenous immunoglobulin has not been studied in polymicrobial NF and should not be recommended.

Other critical supportive measures in the treatment of NF include adequate nutritional support, fluid management, and pain control. Total parenteral therapy should be instituted soon after surgery for adequate provision of caloric substrates and close management of fluid status. Although a causative effect between NSAIDs and NF has not been definitively proved, their use should be limited during NF. Tetanus prophylaxis with a toxoid vaccine and immunoglobulin may be indicated in patients who are not up to date with their immunizations to prevent potential complications from *Clostridium tetani*.

Because of the potential morbidity of invasive streptococcal disease, chemoprophylaxis with penicillin, a first-generation cephalosporin, clindamycin, or erythromycin should be considered in close household contacts with the following risk factors: those younger than 2 years, the elderly, the immunosuppressed (e.g., asplenia, corticosteroid use), those with malignancy, and those with chronic diseases (e.g., diabetes, peripheral vascular disease) (References 79, 90). Immunization with the varicella vaccine is an important method of eliminating risk factors for GAS-related NF in children.

Viral Skin Infections

Herpes Simplex Virus

Herpes simplex viruses (HSVs) belong to the family of human herpes viruses (HHVs), all of which cause a primary infection and remain capable of reactivation later in life. Types 1 and 2 are the most pathogenic, and the two can be distinguished by the dermatologic areas they typically infect. Herpes simplex virus-1 infections tend to occur "above the waist," involving the skin, oral cavity, lips, and face. Herpes labialis is the most common HSV-1 disease (also known as orolabial HSV-1 or gingivostomatitis). Herpes simplex virus-2 infections typically occur in the genital region ("below the waist") in teenagers and adults who are sexually active

(Reference 91). Despite these generalizations, both viruses can cause disease in either area, as evidenced by the increasing incidence of orolabial HSV-2 and genital herpes caused by HSV-1 (Reference 92).

Herpes simplex virus-1 is ubiquitous among humans. Almost 60% to 90% of adults worldwide are infected with HSV-1 and are largely asymptomatic because of long latency periods in healthy individuals (Reference 92). Unlike other childhood viral illnesses, which are acquired during day care or school outbreaks, primary HSV-1 infections occur early in life, between 1 and 3 years of age, likely through close contact with family members who are contagious or on the verge of developing recurrent disease (Reference 92). By preschool age, the prevalence of HSV-1 in children around the world is estimated to be between 17% and 55% (Reference 93).

The prevalence of genital herpes among adults aged 14–69 years is 16.2% (Reference 94). A woman who experiences a primary genital herpes outbreak or recurrence can pass the virus on to her newborn. The incidence of neonatal herpes infection is about 1 in every 3500–20,000 births (Reference 92). The disease carries high morbidity and mortality. Even with treatment, 15% of infants with encephalitis and 57% with disseminated disease die (Reference 95).

Microbiologic Etiology

Herpes simplex virus-1 and -2 are large DNA viruses with genomes that code for a variety of glycoproteins and polypeptides involved in viral replication. After multiplying in the epithelial cells, the virus invades local nerve endings and travels up to the neural cell bodies in the regional sensory ganglia, where it remains dormant until reactivation. The trigeminal ganglion is the most common reservoir for oral-facial HSV-1 infection. Exposure to triggers such as trauma, ultraviolet light, fever, physical and emotional stress, radiotherapy, and organ transplants may result in disease reactivation (Reference 96). Herpes simplex virus shedding from the oral cavity is observed in 2% to 9% of asymptomatic subjects (Reference 93). Transmission of HSV-2 infections can occur through skin contact or bodily fluids, including semen, cervical fluid, or vesicular fluid from active lesions. A person may be contagious even when clinically asymptomatic (Reference 91). The incubation period is typically from 2 days to 2 weeks after exposure (Reference 92).

Clinical Presentation

Primary HSV infection may result in (1) an asymptomatic course, resulting in antibody production; (2) a localized or general eruption; or (3) a serious systemic disease (Reference 97). Most healthy children who contract the herpes virus will present with a prodrome and develop lesions on the skin and mucous membranes in a variety of distributions, including the digits, knees, ear and face, mouth, and genital area (Figure 9 and Figure 10). Symptoms associated with primary infections will always be more severe than those associated with a recurrence. Immunocompromised patients most commonly present with severe local lesions, though disseminated disease with generalized vesicular skin lesions and visceral involvement can also occur (Reference 92). Despite proper treatment, HSV infection acquired during the neonatal period is associated with significant morbidity and mortality because it can disseminate to the liver, lungs, and central nervous system. Skin lesions are present in 60% of cases with disseminated disease and in 85% of localized infection to the skin, eyes, and mouth (Reference 92).

Diagnosis

Most HSV-1 cases may be diagnosed by history and physical examination. Although a positive viral culture obtained from mucous membranes or lesions is considered confirmatory, this is rarely performed. Immunologic assays are better at differentiating between different subtypes and confirming exposure (Reference 92).

Treatment

The cornerstone of therapy is the purine nucleoside analog acyclovir, which limits viral replication but cannot eradicate cells that are already infected. Clinically, this translates into decreases in viral shedding, healing time, and disease severity. Acyclovir is available in oral and intravenous dosage forms, but the oral formulation requires frequent dosing because of its short half-life and poor bioavailability. Oral acyclovir is effective for primary and recurrent genital herpes and orolabial herpes in immunocompetent hosts (References 98, 99). Parenteral acyclovir should be reserved for systemic disease requiring hospitalization, as well as for neonates or immunocompromised patients. Failure to respond to acyclovir may necessitate treatment with intravenous foscarnet, which can cause significant renal toxicity (Reference 91).

Valacyclovir and famciclovir are oral prodrugs to acyclovir and penciclovir, respectively. Their enhanced bioavailability permits less frequent dosing compared with acyclovir. They have efficacy comparable to acyclovir for mucocutaneous herpetic disease but not for systemic infections. In adolescents and adults, these drugs are indicated for primary and recurrent genital herpes and recurrent orolabial herpes (Reference 98). Their use in primary, moderate to severe orolabial herpes is extrapolated from their overwhelming clinical success in treating recurrent disease. Chronic suppressive therapy



Figure 9. Primary herpes simplex virus (HSV) gingivostomatitis in an infant. Images reprinted with permission from Medscape.com, 2011.



Figure 10. Herpes gladiatorum behind the ear. Images reprinted with permission from Medscape.com, 2011.

with these agents for up to 1 year is safe and effective in preventing recurrences and asymptomatic viral shedding in patients prone to frequent outbreaks (Reference 98). Recent studies delineating their pharmacokinetic profiles and dosing recommendations in younger children may potentially allow their use in lieu of acyclovir in orolabial herpes (References 100, 101).

Topical formulations of acyclovir and penciclovir can be used in localized HSV disease to lessen disease severity, viral shedding, and associated discomfort. Topical antivirals are not as consistently effective as oral regimens for genital and orolabial herpes and should not be routinely recommended (Reference 98). Docosanol is a biphenyl alcohol that is available over the counter as a topical cream. When applied early during the prodromal phase, docosanol can help reduce healing time and shorten the duration of painful symptoms in orolabial herpes. Other over-the-counter anesthetics containing benzocaine, lidocaine, tetracaine, benzyl alcohol, camphor, or phenol may provide symptomatic pain relief when applied at the first sign of tingling and burning before orolabial lesion development, but they do not alter the underlying disease course.

Varicella

Chickenpox is a ubiquitous childhood vesicular exanthema caused by the varicella zoster virus (VZV) (Figure 11 and Figure 12). Presentation and prevention with immunization are discussed in the Pediatric Vaccines chapter. Discussion of varicella in this chapter is limited to diagnostic and treatment strategies in children infected with chickenpox.

Diagnosis

Diagnosis of varicella in healthy hosts is based on the appearance of the lesion, confirmed by a history of exposure. Laboratory analysis is not necessary but may reveal an initially depressed white blood cell count, decreased platelet count, and mildly elevated liver function tests. If central nervous system involvement is suspected, cerebrospinal fluid analysis may show mild lymphocytosis, slight elevation of protein, and near-normal glucose levels (Reference 102).

In high-risk patients, rapid confirmation of varicella is important to determine appropriate antiviral therapy. This is best accomplished with immunofluorescence or immunoperoxidase staining for VZV-infected cells obtained from lesion scrapings or an enzyme immunoassay sensitive to VZV antigens present in vesicular fluids. Polymerase chain reaction assays, which can also be performed on vesicular fluid, have a faster, higher yield than viral cultures (Reference 103).



Figure 11. Vesicular rash from varicella zoster (chicken pox). Lesions usually begin on the trunk and spread to the face and limbs. Photo credit: Dr. James Corb, Children's Hospital of Orange County.



Figure 12. Varicella zoster lesions on the face. Photo credit: Dr. John Noble Jr, Centers for Disease Control and Prevention.

Treatment

In healthy children, supportive care is the primary treatment of varicella. Local therapy with drying agents, such as calamine lotion, oatmeal soaks, or Burow solution, can be used on weeping lesions. Topical agents containing antihistamines should be avoided because of the increased risk of percutaneous absorption from loss of skin integrity. Daily baths with soap and water are recommended to destroy the virus's lipid envelope. Acetaminophen should be used for fever and analgesia because antipyretics such as aspirin and NSAIDs have been associated with an increased risk of Reye syndrome and invasive GAS disease, respectively.

Acyclovir is the antiviral drug of choice for treating primary VZV infection. When initiated within 24 hours of the onset of rash, oral acyclovir at 20 mg/kg/dose (maximum 800 mg/dose) four times/day for 5 days was safe and modestly effective in decreasing markers of VZV disease severity (Reference 104). In particular, the clinical benefit seemed more pronounced in children older than 12 years and in secondary household cases that tended to exhibit more serious dermatologic and constitutional symptoms (Reference 102). Because of these observations and the self-limiting nature of VZV, the AAP does not recommend the routine use of antivirals for postexposure prophylaxis or treatment in otherwise young, healthy children; however, acyclovir may be useful for children with complicated disease (pneumonia, encephalitis, or hepatitis) or comorbid conditions (Table 3). Parenteral acyclovir should be initiated in any child who develops severe complications or in any high-risk patient with VZV. Acyclovir doses of 500 mg/m^2 (or a 10-mg/kg/dose in older children) administered every 8 hours for at least 7 days reduce the dissemination of varicella and hasten cutaneous healing in immunosuppressed patients (Reference 102).

Although the efficacy and safety of oral acyclovir is well established in uncomplicated VZV, frequent administration is required because of poor bioavailability. Recent pharmacokinetic data on agents with improved bioavailability such as valacyclovir and famciclovir should greatly simplify dosing regimens and improve adherence (References 100, 101).

Other Viral Exanthems (Hand, Foot, and Mouth Disease; Fifth Disease; and Sixth Disease)

Other common pediatric SSTIs include hand, foot, and mouth disease (HFMD), fifth disease, and sixth disease. These childhood exanthems are typified by a prodrome of fever and constitutional symptoms for several days, followed by the appearance of a characteristic rash in a specific distribution. Diagnosis is largely based on clinical presentation because serology may not always

permit a distinction between previous and recent exposure. Polymerase chain reaction may be useful for confirming primary infection except in sixth disease, where the herpes virus may remain dormant intracellularly. Treatment in otherwise healthy patients consists of supportive management and the occasional use of IVIG or other systemic antivirals in severe systemic disease.

Hand, Foot, and Mouth Disease

Hand, foot, and mouth disease is a highly contagious infection that presents with painful ulcerative lesions in the mouth and rhomboid vesicles ("square blisters") on the palms, soles, and sides of fingers and toes. In the United States, outbreaks of HFMD are typically caused by coxsackievirus A16 or enterovirus 71 (Reference 105). Hand, foot, and mouth disease often occurs as an outbreak among collections of children in a school or child care setting. Incidence is highest during the summer and fall months, with epidemics occurring in 3-year cycles in the United States (Reference 105).

Enteroviruses spread primarily through contact with respiratory droplets or infectious fecal material, though vertical transmission from mother to child is also possible. Because of their resistance to environmental insults, enteroviruses can survive on fomites, adding to their contagiousness (Reference 106). Once infected, patients are contagious until the blisters have resolved (Reference 107).

After the prodrome, patients develop large, painful oral lesions on the palate, tongue, and buccal mucosa in 1–2 days, followed by the presentation of peripheral skin lesions; however, not all patients will express both mucosal and dermatologic symptoms (Reference 106) (Figure 13 and Figure 14). Skin lesions are more commonly found on the dorsal surfaces and may present on the palms, fingers, toes, soles, buttocks, genitals, and limbs. The exanthem begins with red macules that evolve into gray vesicles surrounded by an erythematous halo, but they are not typically pruritic. Cutaneous lesions generally heal without scabbing in 1 week (Reference 108). Complications from coxsackievirus infection include myocarditis, pneumonia, and meningoencephalitis. Recent outbreaks of enterovirus 71 HFMD in Asia have been associated with central nervous system manifestations, particularly encephalitis (Reference 109). In a small case series, treatment with oral acyclovir provided symptomatic relief and improvement in lesions within 24 hours (Reference 110). A trial of acyclovir may be considered in high-risk patients (e.g., immunocompromised hosts or neonates) or outbreaks. Intravenous immunoglobulin has been used

Table 3. Indications for Acyclovir Treatment in Varicella (Reference 102)

Host Status	Treatment	Route
Healthy[a]		
▪ Uncomplicated varicella		
· 2–12 year olds	Optional	Oral
· Secondary household contacts	Beneficial	Oral
· > 12 years old	Highly beneficial	Oral
▪ Complications		
· Viral pneumonia	Indicated	IV
· Encephalitis	Indicated	IV
· Hepatitis	Indicated	IV
▪ Immunocompromised (including malignancy, transplant recipients, congenital immunodeficiency, HIV infection, neonates, steroid therapy)	Indicated	IV
▪ Chronic disease (including cutaneous disorders, pulmonary disorders) ▪ Diabetes mellitus ▪ Disease requiring chronic salicylate or intermittent steroid therapy	Recommended	Oral or IV[b]

[a]Treatment must be initiated within 24 hours after rash for maximal benefit.
[b]Selected patients who are considered at relatively low risk of varicella zoster virus dissemination can be treated by using acyclovir orally with careful monitoring for progression.
IV = intravenous(ly).
Reprinted with permission of Elsevier. Arvin AM. Antiviral therapy for varicella and herpes zoster. Semin Pediatr Infect Dis 2002;13:12–21.



Figure 13. Small vesicles with an erythematous border on the palms and fingers characteristic of hand, foot, and mouth disease. Photo credit: Dr. James Corb, Children's Hospital of Orange County.



Figure 14. Painful oral lesions under the tongue from hand, foot, and mouth disease. Photo credit: Dr. James Corb, Children's Hospital of Orange County.

in patients hospitalized with systemic disease with some beneficial effects, but it should not be used routinely for HFMD (Reference 106).

Erythema Infectiosum (Fifth Disease)

Fifth disease, or erythema infectiosum, is a ubiquitous, benign childhood viral exanthema caused by parvovirus B19, typically affecting children 4–10 years of age. Infection peaks during late winter to early spring, and secondary spread within a household occurs in up to 50% of susceptible individuals (Reference 111). Spread of the virus is primarily through infected respiratory droplets, although transmission by blood products or vertical transmission can occur. The end of the incubation period, ranging from 4 to 14 days, is marked by the formation of immunoglobulin G (IgG) and clearance of viremia, which precedes the characteristic rash. Thus, a patient who exhibits the diagnostic eruptions is not considered contagious (Reference 105).

The rash associated with fifth disease typically develops on the cheeks and appears as if the patient was slapped (Figure 15). The pattern may turn lacy or maculopapular and spread to the proximal extremities or on the trunk. The exanthem may fade and recur when triggered by local irritation, high temperatures, or emotional stress, but this does not represent recrudescence of disease. Arthralgias involving the small joints of the hands, wrists, knees, or ankles can occur in 10% of patients (Reference 111). Transient anemia is a complication that may develop in patients with limited red blood cell reserves, resulting in an aplastic crisis. Parvovirus B19 infection contracted during pregnancy can lead to non-immune hydrops fetalis, a fetal complication resulting in profound anemia, heart failure, and occasionally the death of the fetus in utero (Reference 112). Intravenous immunoglobulins may be considered in chronically immunosuppressed patients with signs of anemia, but they may precipitate the rash and joint symptoms of erythema infectiosum (Reference 105). When symptomatic anemia is present, patients may be supported by blood transfusions.

Roseola (Sixth Disease/Exanthema Subitum)

Roseola, also known as sixth disease or exanthema subitum, is a benign childhood exanthema caused by the 6th and 7th variants of the human herpes virus (HHV). It is one of the most common childhood exanthemas, affecting children between 6 and 18 months of age (Reference 105). Little is known about how the viruses are transmitted, and there seems to be no seasonal predilection for primary infections (Reference 113). Because herpes viruses may remain latent in bodily reservoirs years after the primary infection, the leading hypothesis is that young infants acquire disease through exposure to the saliva or oral secretions of an asymptomatic caretaker who is shedding virus. Vertical transmission of the virus from mother to baby is possible (Reference 114). In addition, HHV-6 can insert its genome into human chromosomes, enabling it to be passed on congenitally (Reference 105).

The classic presentation permitting a clinical diagnosis of primary roseola is fever for 3–5 days that rapidly subsides, followed by the development of a rose-pink maculopapular rash on the neck and trunk that spreads to the extremities and face. Central nervous system complications, including febrile seizures, can occur in up to 15% of primary infections (Reference 112). Examination of the oropharynx may reveal red papules on the soft palate and uvula (Nagayama spots), exudative tonsillar lesions, or herpangina. Other physical findings include mild upper respiratory congestion, otitis media,



Figure 15. Erythematous rash resembling a slapped cheek associated with erythema infectiosum (fifth disease). Photo credit: Centers for Disease Control and Prevention.

nausea, vomiting, cervical and post-occipital lymphadenopathy, and hepatosplenomegaly (References 105, 108). Reactivation from latent disease or reinfection may occur later in life, particularly in immunocompromised individuals such as transplant recipients. Serious manifestations of reactivated HHV-6 include bone marrow suppression, pneumonitis, encephalitis, hepatitis, and organ rejection. Reserved for only severe systemic infection, antivirals such as ganciclovir, foscarnet, and cidofovir show in vitro activity against HHV-6 and have resulted in viral clearance among immunocompromised patients with systemic disease (References 115–117).

Conclusions

Bacterial and viral infections of the skin and soft tissue are common childhood illnesses that are well tolerated by most healthy hosts, but they can develop into severe systemic complications without timely treatment, especially in an immunocompromised patient. The selection of antibiotics for treating bacterial infections must ensure adequate coverage of the most likely organisms based on a patient's risk factors and show favorable absorption and penetration to the infected site. An understanding of local susceptibility patterns is crucial in light of the ever-increasing prevalence of resistant pathogens, such as CA-MRSA. Outpatient regimens with the greatest likelihood of patient acceptance are those that are palatable with simple administration schedules. Parents should be instructed to seek further medical attention if dermatologic and systemic symptoms do not improve within 48 hours. Although parenteral antibiotics should always be administered in a child exhibiting systemic complications from an SSTI, surgical drainage and intervention often plays an integral role in the overall treatment plan of a loculated soft tissue infection or NF. Empiric antibiotics should be narrowed once microbial susceptibilities are available to prevent the evolution of a drug-resistant organism.

Viral skin illnesses are ubiquitous and often acquired early in childhood without significant sequelae. Although the management of viral skin infections is largely supportive, aspirin and NSAIDs should be strictly avoided as antipyretics because of the risk of Reye syndrome and invasive GAS disease, respectively. Antivirals may be indicated in select cases of severe primary or recurrent infections in high-risk populations. Recent pediatric pharmacokinetic data and new drug formulations will allow the use of highly bioavailable antivirals that were previously unavailable to children. A thorough understanding of infectious-related complications and risk factors for more severe disease is important to ensure care is escalated when needed.

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Appendix 1: Pediatric Antibiotic Therapy for Superficial Bacterial Skin Infections

Infection	Pathogen	Daily Oral Dose (Maximal Daily Dose)	Daily Parenteral Dose (Maximal Daily Dose)	Notes
Folliculitis Furuncle Carbuncle	*S. aureus* (CA-MRSA)	**Cephalexin 25 mg/kg/d divided q6h (2 g)** **Dicloxacillin 12 mg/kg/d divided q6h (1 g)** *CA-MRSA coverage:* **Clindamycin 30 mg/kg/d divided q8h (1.35 g)** **TMP/SMX 12 mg/kg/d of TMP divided q12h (640 mg TMP)**[a] Doxycycline 2–4 mg/kg/d divided q12h (200 mg)[b]	**Cefazolin 75 mg/kg/d divided q8h (6 g)** **Oxacillin or nafcillin 150 mg/kg/d divided q4h (12 g)** *CA-MRSA coverage:* **Vancomycin 45–60 mg/kg/d divided q6–8h**[c] **Clindamycin 40 mg/kg/d divided q8h (1.8 g)**	For frequent recurrences, reduce *Staphylococcus* colonization with nasal mupirocin 2% three times/day for 5–10 days. For severe recurrent infections, rifampin 20 mg/kg/d divided q12h plus doxycycline or TMP/SMX for 5–10 days
Erysipelas	GAS	**Cephalexin 25 mg/kg/d divided q6h (2 g)** **Penicillin 50 mg/kg/d divided q6h (2 g)** Erythromycin 40 mg/kg/d divided q6h (1 g) Clindamycin 30 mg/kg/d divided q8h (1.35 g)	**Cefazolin 75 mg/kg/d divided q8h (6 g)** **Penicillin 250,000 units/kg/d divided q4–6h (24 MU)** Azithromycin 10 mg/kg/d divided q24h (500 mg) Clindamycin 40 mg/kg/d divided q8h (1.8 g)	If MSSA coverage desired, consider using first-generation cephalosporin or adding oxacillin in combination with other options
Cellulitis	*S. aureus* (CA-MRSA) GAS	**Cephalexin 25 mg/kg/d divided q6h (2 g)** **Dicloxacillin 12 mg/kg/d divided q6h (2 g)** Erythromycin 40 mg/kg/d divided q6h (1 g) *CA-MRSA coverage:* **Clindamycin 30 mg/kg/d divided q8h (1.35 g)** **TMP/SMX 12 mg/kg/d of TMP divided q12h (640 mg TMP)**[a] Doxycycline 2–4 mg/kg/d divided q12h (200 mg)[b]	**Cefazolin 75 mg/kg/d divided q8h (6 g)** **Oxacillin or nafcillin 150 mg/kg/d divided q4h (12 g)** Ampicillin/sulbactam 200 mg/kg/d of ampicillin divided q6h (12 g of ampicillin) *CA-MRSA coverage:* **Vancomycin 45-60 mg/kg/d divided q6-8h**[c] **Clindamycin 40 mg/kg/d divided q8h (1.8 g)** Linezolid 20-30 mg/kg/d divided q8–12 h (1.2 g)[d]	Consider MRSA coverage if exhibiting systemic illness or no improvement on initial therapy
Bullous impetigo	*S. aureus* (CA-MRSA)	**Cephalexin 25 mg/kg/d divided q6h (2 g)** **Dicloxacillin 12 mg/kg/d divided q6h (1 g)** **Amoxicillin/clavulanate 30-45 mg/kg/day of amoxicillin divided q8–12h (1.75 g of amoxicillin)** Erythromycin 40 mg/kg/d divided q6h (1 g) *CA-MRSA coverage:* **Clindamycin 30 mg/kg/d divided q8h (1.35 g)** **TMP/SMX 12 mg/kg/d of TMP divided q12h (640 mg TMP)**[a]		Topical mupirocin 2% three times/day and retapamulin 1% twice daily for 7 days; recommended for localized disease
Impetigo contagiosa	*S. aureus* (CA-MRSA) GAS			

***Staphylococcus* scalded skin syndrome**	*S. aureus*		**Clindamycin 40 mg/kg/d divided q8h (1.8 g) plus:** **Oxacillin or nafcillin 150 mg/kg/d divided q4h (12 g)** **or** **Cefazolin 75 mg/kg/d divided q8h (6 g)**	For secondary bacterial infection, consider adding age-appropriate gentamicin. Alternatively, Clindamycin plus ceftriaxone IV 100 mg/kg/d divided q12h or cefotaxime IV 150 mg/kg/d divided q8h may be used.
Cutaneous abscess	CA-MRSA	**Clindamycin 30 mg/kg/d divided q8h (1.35 g)** **TMP/SMX 12 mg/kg/d of TMP divided q12h (640 mg TMP)[a]** **Doxycycline 2–4 mg/kg/d divided q12h (200 mg)[b]** Linezolid 20-30 mg/kg/d divided q8–12 h (1.2 g)[d]	**Vancomycin 45–60 mg/kg/d divided q6–8h[c]** **Clindamycin 40 mg/kg/d divided q8h (1.8 g)** Linezolid 20-30 mg/kg/d divided q8–12 h (1.2 g)[d]	Incision and drainage is primary treatment. Continue antibiotics only in high-risk patients. Reserve linezolid for treatment failures because of high cost.
Animal and human bites	*Pasteurella* spp. *Staphylococcus* spp. *Streptococcus* spp. *E.corrodens*, anaerobes	**Amoxicillin/clavulanate 45 mg/kg/d of amoxicillin divided q8–12h (1.75 g of amoxicillin)** Clindamycin 30 mg/kg/d divided q8h (1.35 g) plus: TMP/SMX 12 mg/kg/d of TMP divided q12h (640 mg TMP)[a] or Cefuroxime 30 mg/kg/d divided q12h (1 g) Doxycycline 2–4 mg/kg/d divided q12h (200 mg)[b] Ciprofloxacin 30 mg/kg/d divided q12h (1 g)[e]	**Ampicillin/sulbactam 200 mg/kg/d of ampicillin divided q6h (12 g of ampicillin)** Clindamycin 40 mg/kg/d divided q8h (1.8 g) plus TMP/SMX 12 mg/kg/d of TMP divided q6h (640 mg TMP) Cefoxitin 100 mg/kg/d divided q4–6h (12 g) Meropenem 60 mg/kg/d divided q8h (3 g)	Reserve carbapenems for treatment failure or multidrug resistance.

Bold face signifies first line regimens.

CA-MRSA = community-associated *Staphylococcus aureus*; d = day; GAS = group A β-hemolytic *Streptococcus*; h = hour(s); IV = intravenous(ly); MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; mu = million units; q = every; TMP/SMX = trimethoprim/sulfamethoxazole.

[a] TMP/SMX contraindicated in children < 2 months old.

[b] Doxycycline contraindicated in children < 8 years old.

[c] Titrate vancomycin to trough levels of 10–15 mcg/mL for superficial infections.

[d] Linezolid 10 mg/kg/dose q8h in children <5 years old, 10 mg/kg/dose q12 in children > 5 years

[e] Fluoroquinolones may be used in children if clinically indicated with close monitoring of musculoskeletal adverse effects.

References: Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. Clin Infect Dis 2005;41:1373–406; Gilbert DN, Moellering RC, Eliopoulos GM, Chambers HF, Saag MS, eds. The Sanford Guide to Antimicrobial Therapy. Sperryville, VA: Antimicrobial Therapy, 2009.

Appendix 2: Pediatric Antibiotic Therapy for Deep Bacterial Skin Infections

Infection		Pathogen	Daily Regimen (Maximal Daily Dose)	Notes
Periorbital Cellulitis	***Stye, insect bite, impetigo, eczema***	*S. aureus (especially stye), S. pyogenes*	**Cephalexin PO 50 mg/kg/d divided q6–8h (2 g)** **Dicloxacillin PO 12 mg/kg/d divided q6h (2 g)**	If MRSA suspected, Clindamycin PO 30 mg/kg/d divided q8h (1.35 g) or TMP/SMX PO 12 mg/kg/d (TMP component) divided q12h (640 mg TMP)[a] For severe infection, vancomycin PO 60 mg/kg/d divided q6h (3 g), targeting trough of 15–20 mg/dL
	Complicated rhinosinusitis	*S. pneumoniae, H. influenzae M. catarrhalis*	**Amoxicillin/clavulanate PO 90 mg/kg/d of amoxicillin divided q12h (1.75 g of amoxicillin)** Cefuroxime PO 30 mg/kg/d divided q12h (1 g) Cefdinir PO 14 mg/kg/d divided q12h (600 mg)	Consider Ceftriaxone IV 100 mg/kg/d divided q12 (4 g) if no improvement
	Dental abscess	Mixed aerobic and anaerobic bacteria	**Clindamycin PO 30 mg/kg/day divided q8h (1.35 g)** **Amoxicillin/clavulanate PO 90 mg/kg/d of amoxicillin divided q12h (1.75 g of amoxicillin)** Ampicillin/sulbactam IV 200 mg/kg/d of ampicillin divided q6h (12 g of ampicillin)	
	Hematogenous spread with preceding viral upper respiratory infection	*S. pneumoniae, H. influenzae S. pyogenes, S. aureus*	**Cefotaxime IV 200 mg/kg/d divided q8h (12 g) or Ceftriaxone IV 100 mg/kg/d divided q12h (4 g) plus Clindamycin IV 40 mg/kg/d divided q8h (4.8 g)**	
Orbital cellulitis		*Streptococcus* spp., *H. influenzae S. aureus,* anaerobes	**Ampicillin/sulbactam IV 200 mg/kg/d of ampicillin divided q6h (12 g of ampicillin) or Piperacillin/tazobactam IV 300 mg/kg/d of Piperacillin divided q6h (12 g of ampicillin)** Cefotaxime IV 200 mg/kg/d divided q8h (12 g) or Ceftriaxone IV 100 mg/kg/d divided q12h (4 g) plus Clindamycin IV 40 mg/kg/d divided q8h (4.8 g)	If MRSA suspected, consider vancomycin IV 45–60 mg/kg/day divided q6–8h (3 g), targeting trough 15–20 mg/dL plus Metronidazole IV 30 mg/kg/d divided q8h (4 g) for anaerobic coverage
Necrotizing fasciitis		Monomicrobial: GAS	**Penicillin G IV 400,000 units/kg/d divided q4h plus Clindamycin IV 40 mg/kg/d divided q8h (4.8 g)**	
		Polymicrobial: *S. aureus* Enterics and anaerobes	**Cefotaxime IV 200 mg/kg/d divided q8h (12 g) or ceftazidime IV 150 mg/kg/d divided q8h (6 g) plus Clindamycin IV 40 mg/kg/d divided q8h (4.8 g) or Metronidazole IV 30 mg/kg/d divided q8h (4 g)** Ampicillin/sulbactam IV 200 mg/kg/d of ampicillin divided q6h (12 g of ampicillin) or Piperacillin/tazobactam IV 300 mg/kg/d of Piperacillin divided q6h (12 g of piperacillin) plus Clindamycin IV 40 mg/kg/d divided q8h (4.8 g) plus Ciprofloxacin IV 30 mg/kg/d divided q12h (800 mg)[b] Oxacillin or nafcillin IV 150 mg/kg/d divided q4h (12 g) Meropenem IV 60 mg/kg/d divided q8h (6 g)	Aminoglycosides can be considered if additional gram-negative coverage required. Pseudomonal coverage should be considered in immunosuppressed patients.

Bold face signifies first line regimens.
CA-MRSA = community-associated MRSA; d = day; GAS = group A β-hemolytic *Streptococcus*; h = hours; IV = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*; PO = orally; q = every; TMP/SMX = trimethoprim/sulfamethoxazole.
[a]TMP/SMX contraindicated in children < 2 months old.
[b]Fluoroquinolones may be used in children if clinically indicated with close monitoring of musculoskeletal adverse effects.

References: Stevens DL, Bisno AL, Chambers HF, Everett ED, Dellinger P, Goldstein EJ, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections. Clin Infect Dis 2005;41:1373–406; Gilbert DN, Moellering RC, Eliopoulos GM, Chambers HF, Saag MS, eds. The Sanford Guide to Antimicrobial Therapy. Sperryville, VA: Antimicrobial Therapy, 2009; Vayalumkal JV, Jadavji T. Children hospitalized with skin and soft tissue infections. Pediatr Drugs 2006;8:99–111; Hauser A, Fogarasi S. Periorbital and orbital cellulitis. Pediatr Rev 2010;31 242–9.

Appendix 3: Pediatric Antiviral Therapy for Common Skin Infections

Drug	Daily Oral Dosing (Maximal Daily Dose)	Daily Parenteral Dosing	Notes
Acyclovir	HSV (orolabial and genital, initial) - Children: 15 mg/kg/dose five times/day up to 80 mg/kg/day for 7 days (1 g) HSV (orolabial and genital, episodic/suppressive) - Children: 15 mg/kg/dose two to five times/day up to 80 mg/kg/day for 5 days (1 g) VZV- Children: 20 mg/kg/dose four times/day for 5 days (3.2 g)	HSV - Neonates: 20 mg/kg/dose q8h HSV - Children: 5–10 mg/kg/dose q8h or 250–500 mg/m^2/dose q8h[a] VZV - Children: 10 mg/kg/dose or 500 mg/m^2/dose q8h	Dose obese patients by ideal body weight. Maintain good hydration status to avoid renal toxicity. Dose adjust for renal impairment.
Valacyclovir	Genital herpes (initial) - Adolescents: 1 g/dose twice daily for 7 days Genital herpes (episodic/suppressive) - Adolescents: 1 g/dose daily for 5 days VZV- Children: 20 mg/kg/dose three times/day for 7 days (3 g)		Prodrug of acyclovir
Famciclovir	Genital herpes (initial) - Adolescents: 250 mg/dose three times/day for 7 days Genital herpes (episodic/suppressive) - Adolescents: 125–250 mg/dose twice daily for 5 days VZV - Adults: 500 mg/dose three times/day for 7 days[b]		Prodrug of penciclovir
Foscarnet		Children and adults: 40 mg/kg/dose q8–12h	For acyclovir-resistant HSV/VZV infection only. Maintain good hydration status to avoid renal toxicity. Dose adjust for renal impairment.

HSV = herpes simplex virus; VZV = varicella zoster virus.

[a]Children < 12 years old can receive 30 mg/kg/day, > 12 years old can receive 15 mg/kg/day.

[b]For weight-based pediatric dosing recommendations for famciclovir see Saez-Llorens X, Yogev R, Arguedas A, Rodriguez A, Spigarelli MG, De Leon Castrejon T, et al. Pharmacokinetics and safety of famciclovir in children with herpes simplex or varicella zoster virus infection. Antimicrob Agents Chemother 2009;53:1912–20.

References: Kimberlin DW, Jacobs RF, Weller S, van der Walt JS, Hietman CK, Man CY, et al. Pharmacokinetics and safety of extemporaneously compounded valacyclovir oral suspension in pediatric patients from 1 month through 11 years of age. Clin Infect Dis 2010;50:221–8. American Academy of Pediatrics. Herpes simplex. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. Red Book: 2009 Report of the Committee on Infectious Diseases, 28th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2009.363–73 and 714–27.

CHAPTER 42

Human Immunodeficiency Virus

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Learning Objectives

1. Explain the routes of transmission for human immunodeficiency virus (HIV).
2. Describe the life cycle of HIV.
3. Identify signs and symptoms of acute and chronic HIV infection, including the most common opportunistic infections.
4. Recommend appropriate prophylaxis for common opportunistic infections.
5. Identify goals of therapy for children with HIV infection and recommend appropriate antiretroviral (ARV) therapy for treatment-naive HIV-infected children.
6. Describe efficacy parameters and adverse effects of ARV therapy.
7. Describe the importance of adherence to ARV therapy and strategies to improve adherence for HIV-infected children.
8. Summarize important clinical caveats in pediatric HIV infection.

Abbreviations in This Chapter

AIDS	Aquired immunodeficiency syndrome
ARV	Antiretroviral
cART	Combination antiretroviral therapy
CMV	Cytomegalovirus
EIA	Enzyme immunoassay
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
MAC	*Mycobacterium avium* complex
MTCT	Mother-to-child-transmission
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OI	Opportunistic infection
PCP	*Pneumocystis jiroveci* pneumonia
PCR	Polymerase chain reaction
PI	Protease inhibitor
TDM	Therapeutic drug monitoring

Introduction

This chapter describes the current epidemiology of HIV, the genetic diversity of the virus, and the ways in which it affects the immune system, emphasizing prominent reservoirs of latent viral infection. We will discuss common routes of transmission, identifying signs and symptoms of acute and chronic HIV infection. Pertinent surrogate markers for HIV and the ways in which they pertain to HIV disease progression and the importance of resistance testing will be explained. Because more than 20 ARVs are available, we will focus on the goals of treatment, including nonpharmacologic and pharmacologic approaches for treating HIV infection, with special attention on medication adherence. At the conclusion of this chapter, the reader will appreciate the complexity of the disease and have a clearer and more complete understanding of how to care for and optimize ARV treatment among HIV-infected children and adolescents.

Epidemiology

Human immunodeficiency virus affects about 33.3 million people worldwide (Reference 1). About two-thirds of the global burden of disease exists in sub-Saharan Africa. According to the World Health Organization (WHO), in 2009 there was a reported 2.5 million children (younger than 15 years) living with HIV globally, with an incidence of 370,000 new HIV infections and 260,000 deaths secondary to AIDS (Reference 1). Almost 15% of these new HIV infections were in children younger than 15 years, and an additional 41% of these infections occurred among young people 15–24 years of age. In 2009, among 40 states with confidential name–based HIV infection reporting, the estimated number of diagnoses of HIV infection among children younger than 13 years was 166; by contrast, there were 21 cases in the 13- to 14-year-old group and 2036 cases in the 15- to 19-year-old group (Reference 2).

Human immunodeficiency virus exists as two different virus types: HIV-1 and HIV-2. Human immunodeficiency virus type 1 is much more common worldwide than HIV-2. The first cases of HIV-1 infection were reported in the United States in 1981 among homosexual men in San Francisco, California (Reference 3). Human immunodeficiency virus type 1 is extremely diverse in its genetic composition and is classified into three groups: M, N, and O. The M group, which is the most common, consists of 11 different subtypes or

clades designated by the letters A–K. The geographic distribution of these different subtypes varies; for example, subtype B is common in the United States, and subtype C is common in South Africa.

In 1986, HIV-2 was isolated from patients with AIDS in West Africa, where it is still predominantly found. Most of the world's remaining burden of HIV-2 infection is reported among countries with strong socioeconomic ties to West Africa such as France, Spain, Portugal, and former Portuguese colonies Brazil, Angola, Mozambique, and parts of India near Goa. Although HIV-2 has modes of transmission similar to HIV-1, it is less virulent than HIV-1, and disease progresses more slowly. Human immunodeficiency virus type 2 infections, compared with HIV-1, results in comparatively lower viral loads, less transmission, and fewer AIDS cases (Reference 4).

Etiology

Pathophysiology

Human immunodeficiency virus type 1 belongs to the lentivirus subfamily of retroviruses. It is a single-stranded RNA virus that uses reverse transcriptase to produce proviral DNA required for virus replication and persistent infection of $CD4^+$ cells. Human immunodeficiency virus type 1 consists of nine separate genes that are divided into three classes: structural proteins that encode for the viral core, enzymes for viral replication and integration and for the structure of the viral envelope; regulatory proteins involved with viral transcription and protein synthesis; and accessory proteins.

During acute infection, HIV specifically infects $CD4^+$ cells. Human immunodeficiency virus entry into the $CD4^+$ cells is a multistep process. First, gp120, a trimer envelope glycoprotein on the HIV virion, binds to the $CD4^+$ cell receptor. Once bound, a conformational change occurs in gp120, allowing additional binding to one of the co-receptors on the $CD4^+$ cell: CCR5 or CXCR4. The CCR5 co-receptor is associated with early infection, and the CXCR4 co-receptor is more commonly found in treatment-experienced patients or in those with advanced stages of HIV disease. CCR5 antagonists, such as maraviroc, bind to the CCR5 co-receptor, which thereby prevents HIV binding and subsequent fusion of the viral envelope and the cell membrane.

Once the HIV virion binds to one of the co-receptors, it enables the trimer gp41 to bind to the $CD4^+$ cell membrane, facilitating the fusion of the virion with the $CD4^+$ cell. The HIV entry inhibitor enfuvirtide is a fusion inhibitor that binds to gp41 and prevents fusion of the HIV virion with the $CD4^+$ cell membrane. Uncoating of the capsid releases single-stranded HIV RNA into the cytoplasm of the $CD4^+$ cell. This is then transcribed into double-stranded HIV DNA by HIV reverse transcriptase. Human immunodeficiency virus reverse transcriptase is highly error prone with no proofreading mechanism, permitting the evolution of several mutations in HIV RNA as viral replication continues, thus contributing to its genetic variation. Nucleoside reverse transcriptase inhibitors (NRTIs) are nucleoside analogs that must be triphosphorylated (except for tenofovir, which is a nucleotide and requires only two additional phosphorylations) before incorporation by reverse transcriptase into the HIV DNA chain. These NRTIs then act as DNA chain terminators, inhibiting further synthesis of HIV DNA. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) also inhibit reverse transcriptase by binding directly to the enzyme, creating structural alterations that prevent the addition of nucleosides to the growing DNA chain.

Double-stranded HIV DNA is then transported to the nucleus and integrated into the genome of the $CD4^+$ cell as proviral HIV DNA virus by HIV integrase. Integrase strand transfer inhibitors such as raltegravir prevent HIV integrase from inserting HIV proviral DNA into the host cell's DNA. Human immunodeficiency virus proviral DNA virus is representative of latent HIV viral reservoirs. Common sites of latent reservoir infection primarily include lymphoid tissue, as well as peripheral blood dendritic cells and monocytes, resting $CD4^+$ lymphocytes, and microglial cells of the central nervous system, reproductive tract, and gastrointestinal tract. The establishment of these latent reservoirs of infection serves as one of the primary reasons for the difficulty in finding a cure for HIV (Reference 5).

Once the proviral HIV DNA is activated in the $CD4^+$ cell, it is transcribed and translated into a polyprotein, which is cleaved by HIV protease into several different smaller proteins or subunits that are responsible for assembling a new, mature HIV virion. Protease inhibitors (PIs) bind HIV protease, preventing the cleavage of the polyprotein into individual proteins, which makes the assembly of a mature and infectious HIV virion unlikely. This new HIV virion then buds off from the infected $CD4^+$ cell and infects another $CD4^+$ cell. The life cycle of HIV infection and replication described above is repeated 1–10 billion times/day.

Genetic Basis

The CCR5 co-receptor is a common host factor important for HIV transmission and pathogenesis. Not only do $CD4^+$ cells have CCR5 co-receptors, but these co-receptors can also exist on macrophages. Therefore, HIV can also infect macrophages, which seem to act as one of the primary sources responsible for HIV transmission into the brain. About 3% to 5% of patients with HIV infection can remain asymptomatic, maintaining normal $CD4^+$ cell counts for several years without

ARV therapy; these are termed *long-term nonprogressors*. About 1% of HIV-infected patients will have undetectable viral loads with maintenance of high $CD4^+$ cell counts; these are termed *elite controllers* (References 6–8). Slow HIV disease progression in these patients may occur because of varying genotypes of the 32-bp deletion (Δ32) in the CCR5 co-receptor. Some patients who are homozygous for the CCR5 Δ32-bp deletion do not express the co-receptor on $CD4^+$ cells and are consequently resistant to HIV infection (Reference 9). Those heterozygous for this CCR5 genetic mutation have slower disease progression than individuals without the mutation. Other genetic polymorphisms that may influence HIV infection and the rate of disease progression include *APOBEC3G*, *HLA-*B27*, and *HLA-*B57* (Reference 10).

Risk Factors

One of the primary risk factors for HIV infection is the transmission of HIV from mother to child (also known as mother-to-child-transmission [MTCT]). In 2009, the estimated number of new diagnoses of HIV from MTCT in the United States was 131 (Reference 11). The transmission risk of passing HIV from an untreated HIV-infected mother to the fetus is about 20%. In these cases, elective cesarian section may be a suitable option to significantly reduce the rates of MTCT. For those who are taking ARVs and have excellent virologic control (defined as an undetectable viral load of less than 20–75 copies/mL), the risk of MTCT is reduced to less than 1% to 2%. Refer to Table 1 for a comprehensive list of other risk factors (including more common and less common) for HIV transmission (References 12–16).

Clinical Presentation and Diagnosis

Signs and Symptoms

Infants and children infected with HIV often show signs of developmental delay (late to develop motor skills and cognitive ability). Weight gain or growth during the first year of life (failure to thrive) is usually absent. Children with HIV may also develop opportunistic infections (OIs) or conditions that further affect growth and development. Human immunodeficiency virus encephalopathy can lead to microcephaly or brain atrophy. Motor impairments, such as gait abnormalities and ataxia, may also occur (Reference 17). *Candida* infections (such as mucosal oropharyngeal thrush, vaginitis, and invasive

Table 1. Risk Factors for HIV Transmission (References 12–16)

Risk Factor	Comment
More Common	
Breastfeeding	Can be as high as 42% risk, depending on the breastfeeding duration (Reference 12)
Injection drug use	Needle exchange programs and methadone maintenance programs have been shown to reduce the risk of HIV transmission (References 13, 14).
Unprotected vaginal or anal sex	Men who have sex with men who engage in unprotected receptive anal sex have the highest risk of transmission.
Multiple sex partners	Presence of other sexually transmitted infections (e.g., herpes simplex, syphilis) can increase the risk of HIV infection during sex.
Substance abuse	Alcohol, crack cocaine, crystal methamphetamine, and opioids can lead to high-risk sexual behavior.
Less Common	
Use of contaminated needles or sharps	Needlestick or sharp object injury to a health care worker
Receipt of contaminated blood products	Through blood transfusion, organ/tissue transplantation
Unprotected oral sex	Carries a lower risk than unprotected vaginal or anal sex
Receipt of pre-chewed food	Feeding infants with food that is pre-chewed by an HIV-infected person (Reference 15)
Being bitten by an HIV-infected person or deep or open-mouth kissing with an HIV-infected person whose mouth or gums are bleeding	HIV cannot reproduce outside the human body and is not spread by air or water; mosquitoes; saliva, tears, or sweat; shaking hands or sharing dishes; or closed-mouth or "social" kissing (Reference 16).

esophageal candidiasis), cytomegalovirus (CMV), and *Pneumocystis jiroveci* pneumonia (previously termed *P. carinii* pneumonia [PCP]) are common OIs and will be discussed below. Children with HIV infection are also prone to recurrent bacterial infections and to lymphoid interstitial pneumonia, which is rare in the adult population (References 18, 19).

Acute HIV infection in adolescents who are infected through high-risk behaviors, such as sharing needles or unprotected sexual contact, may present with nonspecific symptoms, including fever, headache, sore throat, joint and/or muscle pain, lymphadenopathy, and generalized rash (References 20–24). This acute retroviral syndrome typically occurs 2–4 weeks after infection. The persistence of these symptoms in the presence of ulcers on the mucosa of the mouth, anus, genitalia, or esophagus is suggestive of HIV infection. Gastrointestinal disturbances such as nausea, diarrhea, weight loss, and loss of appetite may also occur. Signs and symptoms of chronic HIV infection include continued weight loss, fatigue, recurrent yeast infections (vaginal or oral), and skin abnormalities (frequent rashes, psoriasis) (Reference 21).

Opportunistic Infections

P. jiroveci pneumonia is one of the most common OIs diagnosed in HIV-infected children, with the highest rates of occurrence in infants up to 12 months old. The risk of PCP infection increases with a decrease in $CD4^+$ count and $CD4^+$ percentage. Distinguishing features of infection include fever, cough, dyspnea, and tachypnea. Pediatric patients typically also present with low oxygen saturation, a $CD4^+$ count below 200 cells/mm^3, and/or a $CD4^+$ percentage less than 15% in children older than 5 years. Chest radiographs may be normal, show little infiltrate, or show bilateral parenchymal infiltrates. Although elevated lactate dehydrogenase and decreased serum albumin may also be present, they are not specific to PCP infection. To diagnose PCP, the organism must be identified in pulmonary tissue, preferably obtained by bronchoscopy with bronchoalveolar lavage. *Pneumocystis* organisms may be recognized through staining: methenamine-silver and toluidine blue stain the cyst wall, but immunofluorescent antibodies, which also stain the cyst wall, have higher specificity. Prophylaxis against PCP is highly recommended in children 1–12 months of age regardless of $CD4^+$ count, in children 1–5 years of age with $CD4^+$ counts less than 500 cells/mm^3 or $CD4^+$ percentage less than 15%, and in children 6 years or older with $CD4^+$ counts less than 200 cells/mm^3 and/or $CD4^+$ percentage less than 15%. Primary prophylaxis should not be discontinued in patients younger than 1 year, but it may be discontinued in older children after they have received ARV treatment for at least 6 months and have met the following $CD4^+$ count thresholds: children 1–5 years of age: $CD4^+$ count of 500 cells/mm^3 or greater for more than 3 consecutive months; children 6 years and older: $CD4^+$ count of 200 cells/mm^3 or greater for more than 3 consecutive months (Reference 25).

Mycobacterium avium complex (MAC) is another common OI among HIV-infected children. The risk of infection increases with varying levels of age-specific immunosuppression (see Table 2). *M. avium* complex colonizes the gastrointestinal and respiratory tracts; its presence in these locations can be predictive of DMAC (disseminated infection), which can involve the lungs, lymph nodes, liver, spleen, and bone marrow (Reference 26). Respiratory symptoms are rare, but cough may be present. Common signs and symptoms include fever, weight loss, muscle weakness, abdominal pain, diarrhea, chills, night sweats, fatigue, and hepatosplenomegaly. Laboratory findings reveal anemia, neutropenia, and thrombocytopenia and may include elevated lactate dehydrogenase or alkaline phosphatase values. A blood culture or bone marrow biopsy is required for a diagnosis of MAC. Although a positive acid-fast bacillus test may be indicative of MAC in a symptomatic patient, it cannot be distinguished from *Mycobacterium tuberculosis* without a culture or confirmation with a polymerase chain reaction (PCR) test. As with PCP, prophylaxis against MAC is highly recommended in patients meeting certain $CD4^+$ counts or $CD4^+$ percentage thresholds (Table 2). Prophylaxis is indicated in the following situations: in infants with $CD4^+$ counts less than 750 cells/mm^3; in children 1–2 years of age with $CD4^+$ counts less than 500 cells/mm^3; in children 2–5 years of age with $CD4^+$ counts less than 75 cells/mm^3; and in children 6 years and older with $CD4^+$ counts less than 50 cells/mm^3. Primary prophylaxis should not be discontinued in patients younger than 2 years, but it may be discontinued in older children after they have received ARV treatment for at least 6 months and have met the following $CD4^+$ count thresholds: children 2–5 years of age: $CD4^+$ count greater than 200 cells/mm^3 for more than 3 consecutive months; children 6 years and older: $CD4^+$ count greater than 100 cells/mm^3 for more than 3 consecutive months (Reference 25).

Toxoplasma gondii infection in infants and children is usually the result of maternal infection present before or at birth. In older children and adolescents, acquisition is typically through ingesting parasite-containing raw or undercooked meat or water or soil contaminated with sporulated oocysts. Because cats are confirmed hosts for *T. gondii* and may excrete sporulated oocysts in their feces after early infection, contact with their feces can also be a risk factor for infection. In patients with AIDS, *T. gondii* usually presents with central nervous system effects, including headache, confusion, neurologic deficiencies, and seizures. Fever may be present, and nausea or vomiting can occur with significant mental

status changes. Diagnosis is confirmed by enzyme immunoassay (EIA) testing for immunoglobulins specific to *Toxoplasma* (immunoglobulin A, E, or M up to 6 months of age or G after 1 year of age). Children older than 5 years with $CD4^+$ counts below 100 cells/mm^3 and positive antibody tests should receive prophylaxis for *T. gondii*; children 5 years and younger with positive antibody testing should receive prophylaxis if the $CD4^+$ percentage is below 15%. Primary prophylaxis should not be discontinued in patients younger than 1 year, but it may be discontinued in older children after they have received ARV treatment for at least 6 months if they meet the following $CD4^+$ count thresholds: children 1–5 years of age: $CD4^+$ percentage of 15% or greater for more than 3 consecutive months; children 6 years and older: $CD4^+$ percentage of 15% or greater or $CD4^+$ count greater than 100–200 cells/mm^3 for more than 3 consecutive months (Reference 25).

Cytomegalovirus may be transmitted perinatally by ingesting CMV-containing bodily fluids (blood, breast milk, saliva, genital secretions) or through sexual contact. The risk of infection is highest during the first year of life. Symptoms of disease include microcephaly, hearing impairment, hepatosplenomegaly, and retinitis, which may be characterized by blurred vision or blind spots. Photopsia is highly associated with CMV retinitis in patients with AIDS (Reference 27). Many children with CMV at birth subsequently acquire developmental

Table 2. Primary Prophylactic Drug Regimens for Common Opportunistic Infections in HIV-Infected Children and Adolescents (Reference 25)

Pathogen	Indication for HIV-Infected Children	Preferred Prophylaxis Regimen(s): Children	Preferred Prophylaxis Regimen(s): Adolescents
Pneumocystis jiroveci pneumonia (PCP)	Age 1–12 months Age 1–5 years with $CD4^+$ < 500 cells/mm^3 or CD4% < 15% Age 6–12 years with $CD4^+$ < 200 cells/mm^3 or CD4% < 15% Adolescents with $CD4^+$ < 200 cells/mm^3 or CD4% < 14%	Trimethoprim/sulfamethoxazole (TMP/SMX)[a]: 150/750 mg/m^2 of body surface area per day, given as: Two divided doses daily OR three times/week OR As a single dose three times/week on consecutive days MDD: 320/1600 mg	TMP/SMX: 160/800 mg once daily OR 160/800 mg three times/week OR 80/400 mg once daily
Mycobacterium avium complex (MAC)	Age < 1 year with $CD4^+$ < 750 cells/mm^3 Age 1–2 years with $CD4^+$ < 500 cells/mm^3 Age 2–5 years with $CD4^+$ < 75 cells/mm^3 Age ≥ 6 years with $CD4^+$ < 50 cells/mm^3	Clarithromycin: 7.5 mg/kg twice daily MDD: 1000 mg Azithromycin: 20 mg/kg once weekly Maximum weekly dose: 1200 mg	Azithromycin: 1200 mg once weekly OR 600 mg twice weekly Clarithromycin: 500 mg twice daily
Toxoplasma gondii	*Toxoplasma* Antibody(+), PLUS: Age < 6 years with CD4% < 15% OR Age ≥ 6 years with $CD4^+$ < 100 cells/mm^3	TMP/SMX: 150/750 mg/m^2 body surface area per day, given as: Two divided doses daily OR three times/week OR As a single dose three times/week on consecutive days MDD: 320/1600 mg	TMP/SMX: 160/800 mg once daily

[a]Patients who are allergic to sulfonamide antibiotics may take dapsone as an alternative to TMP/SMX for PCP prophylaxis; if so, they should be monitored for signs of cross-sensitivity. Additional alternatives to TMP/SMX include aerosolized pentamidine and atovaquone.
MDD = maximum daily dose; TMP/SMX = trimethoprim/sulfamethoxazole.

delays, neurologic deficits, learning disabilities, ophthalmologic complications, or seizure disorders. Similar to HIV infection, CMV is difficult to diagnose in infants with antibody testing because maternal antibodies may be present throughout the first year of life. In children older than 12 months, a positive antibody test does not always indicate an active infection, but it is indicative of CMV exposure. Cytomegalovirus may be detected by culture or a polymerase chain reaction test. Primary prophylaxis for CMV is not routinely recommended; however, yearly screenings are recommended for children who tested negative at birth and for children whose $CD4^+$ counts are below 100 cells/mm^3 or who have a $CD4^+$ percentage below 10% (Reference 25).

Candida infections are common among HIV-infected children and are most often caused by *Candida albicans*. These infections are found in the mucosa of the oral cavity, esophagus, and oropharynx (thrush, angular cheilitis) and as dermatitis in the diaper area; they may also be found in the vulvovaginal area of adolescent girls. Infants and toddlers with *Candida* infection may present with discomfort in the diaper area or difficulty/pain on swallowing. *Candida* infection can be diagnosed with a biopsy of infected tissue (for staining or culture); invasive disease, although not typically a significantly high-risk issue in HIV-positive patients, may be diagnosed by blood culture. Although a low $CD4^+$ count, less than 100 cells/mm^3, increases the risk of developing a *Candida* infection, primary prophylaxis is rarely recommended because active infections respond well to existing treatment measures. Initiating antifungal prophylaxis also increases both the risk of developing antifungal drug resistance and the potential for drug-drug interactions with ARV medications (Reference 25).

Table 2 provides a summary of recommended prophylaxis regimens for PCP, MAC, and toxoplasmosis. There are resources available that provide greater detailed information on alternative primary prophylaxis regimens, secondary prophylaxis, discontinuation of prophylaxis, and the treatment of active infection in HIV-positive children and adolescents (References 25, 28, 29).

Diagnostic Criteria

Laboratory Data

Human immunodeficiency virus infection is diagnosed by several methods, including detection of viral antibodies, the p24 antigen, or HIV genetic material. Standard antibody testing is performed using EIA. Because of their high sensitivity and somewhat low specificity, positive EIA results must be confirmed by a Western blot, which uses antibodies to identify specific proteins after they are separated by gel electrophoresis. A negative EIA is typically considered a true negative; however, a false-negative result is possible if the test is performed in the "window period" of acute infection (i.e., the time it takes the body to produce antibodies to HIV). For indeterminate results, a repeat EIA is recommended as well as HIV RNA testing. Antibody testing may be performed by standard or rapid testing methods. Rapid tests offer the following advantages: the result can be read by a counselor/provider while the patient remains on-site (results can be available in 40 minutes or less); patients can receive an immediate offer of or referral to medical care and/or counseling services; and these tests are performed using blood, plasma, serum, or saliva samples (References 30, 31). The immediate results obtained from rapid testing have allowed more patients to be made aware of their infection status and expedited the care of patients with newly diagnosed HIV infection (References 32, 33). Many commercially available rapid tests can identify both HIV-1 and HIV-2. It is recommended to confirm a positive rapid test result with both the standard EIA and the Western blot tests. Criteria for interpreting a Western blot result have been offered by several national and international agencies, including the CDC and WHO. The CDC criteria for a positive result include reactivity to either the gp41 or the p24 antigen, in addition to the gp120/160 antigens.

A PCR test, a DNA test, or nucleic acid amplification can detect HIV antigens or isolate the virus. These methods are most useful to identify infection for those in the "window period" or for the diagnosis of HIV in infants. Virologic testing (for the presence of HIV RNA), rather than antibody testing, is recommended in infants because of the presence of maternal antibodies transferred by the placenta. Human immunodeficiency virus virologic testing should be performed in exposed infants within 14–21 days of birth, at 1–2 months old, and at 4–6 months old. Consideration may be given to performing the first round of testing at birth in infants who are at high risk of HIV infection, such as those born to mothers who did not receive antepartum ARV therapy for the prevention of MTCT or whose mothers did not have a viral load less than 1000 copies/mL at delivery. An infant with an initial negative virologic test should be retested at 1–2 months of age. Although infants should complete a 6-week course of zidovudine prophylaxis against HIV, this has not been shown to alter the time to detect HIV or alter the sensitivity of the testing method. A third virologic test is recommended at 4–6 months of age in infants who have two previously negative tests to ultimately rule out the presence of HIV infection. Although not recommended at birth, two sets of negative antibody tests performed at a minimum of 6 months of age may also rule out HIV infection in children in the absence of other clinical or virologic signs of infection. Antibody testing is also considered at 12–18 months of age in patients with previous negative virologic testing to confirm that maternal antibodies are no longer present. Human

immunodeficiency virus infection may be diagnosed by antibody testing and confirmatory Western blot in children 18 months and older (Reference 28).

Course and Prognosis of Disease

The highest risk of disease progression is in children younger than 5 years, regardless of immunologic status; there is a 4-fold increased risk of progressing to AIDS and a 6-fold increased risk of death for a 1-year-old child than for a child 5 years or older at a similar $CD4^+$ percentage. Children who are at least 5 years old have a 12-month risk of death or progression to AIDS similar to that of young adults (around 20 years old), at $CD4^+$ counts less than 350 cells/mm^3 (References 28, 34). The difference in risk of disease progression and death between these age groups is likely multifactorial. High levels of HIV RNA can persist for a longer period in younger children, and although viral load levels may be low at birth, they can increase substantially by 2 months of age to more than 100,000 copies/mL. The risk of HIV progressing to AIDS increases when viral loads are above this threshold. In addition, a young child's developing immune system may not be robust enough to limit viral replication.

The virologic set point is the level of HIV RNA that is reached after a decline in viral load after acute infection; this level is typically set about 6–12 months after infection and shows a correlation with the risk of disease progression or death in adolescent patients. The application of this information to infants and young children is less clear because of the fluctuations in HIV viral load seen in this population. In infants, high viral loads (greater than 299,000 copies/mL) are associated with a greater risk of disease progression and death (References 35, 36). This increased risk is also present for adolescents with viral loads higher than 100,000 copies/mL (References 37, 38). The risk of progression to AIDS and death in children is greatest in the first year of life regardless of HIV RNA level, with the risk increasing at higher viral loads (Reference 39). Given the potential for fluctuating HIV RNA levels in very young children as mentioned previously, it is important to consider both the immunologic and virologic status of a child when determining his or her risk of disease progression (Reference 40).

Treatment

Goals of Therapy

Human immunodeficiency virus is a chronic infection that requires lifelong therapy. Therefore, the goals of ARV treatment for HIV-infected children and adolescents are to reduce HIV-related mortality and morbidity, preserve and restore immune function, achieve virologic suppression, prevent the emergence of drug resistance, minimize ARV adverse effects, maintain normal physical growth and neurocognitive development, and improve quality of life (Reference 28).

Nonpharmacologic Therapy

Micronutrient (multivitamin and trace element) deficiencies are common in HIV-infected patients, especially those with advanced disease progression and those living in developing countries. Therefore, vitamin supplementation has been explored as an avenue for reducing HIV disease burden. A Cochrane review analysis showed that several micronutrient supplements reduced mortality and morbidity in HIV-infected pregnant women and their children (Reference 41). Multivitamin supplementation in African pregnant patients has also been associated with decreased adverse pregnancy outcomes such as fetal death, low birth weight, and severe preterm births. The children also had better growth, better micronutrient status, and higher $CD4^+$ counts in the first 6 months to 2 years of life (References 41, 42). As a whole, multivitamin supplementation seems to be beneficial to HIV-infected patients and may also serve as an indicator for assessing adherence to medications before considering the initiation of ARVs.

Herbal Therapy

Herbals may also play a role in the treatment of HIV infection. The catechins contained in green tea have been associated with several health benefits (Reference 43). In vitro studies have shown that epigallocatechin gallate (EGCG), the most plentiful catechin in green tea, inhibited gp120 of the HIV virion binding to the $CD4^+$ cell receptor (Reference 44). However, studies of EGCG suggest that a significant quantity of green tea would need to be consumed to produce an in vivo effect (References 45, 46). Other potentially beneficial herbals include *Hypoxis hemerocallidea* (African potato) and *Sutherlandia frutescens*. The African potato is used as an immune-stimulant and has antioxidant properties. *Sutherlandia* possesses a constituent L-canavanine, which is thought to have antiviral activity.

One disadvantage of the *Hypoxis* and *Sutherlandia* spp. is the potential for drug interactions with ARVs because they may inhibit the cytochrome P450 (CYP) 3A4 isoenzyme (CYP3A4) and P-glycoprotein (an efflux transporter). Other herbals such as St. John's wort (*Hypericum perforatum*) or garlic supplements are inducers of CYP3A4 and may decrease the serum concentrations of the PIs, NNRTIs, and maraviroc (Reference 47). Health care providers, especially pharmacists, are encouraged to ask patients about vitamin supplementation and herbal use to rule out any potential drug interactions with ARVs. Furthermore, another major

limitation to using herbals for treating HIV infection is the lack of U.S. Food and Drug Administration (FDA) regulation and approval based on efficacy and safety. Thus, caution should be taken if HIV-infected children are using herbals and ARVs concomitantly.

Prevention

One of the best ways to prevent HIV transmission is to use safe sex practices such as condoms. When latex condoms are used consistently and correctly, they are highly effective in preventing sexual transmission of HIV. One study found that consistent condom use resulted in an 80% reduction in HIV incidence in HIV serodiscordant heterosexual couples (Reference 48). A review study also showed that among men who have sex wih men (MSM), condom use reduced the per-contact risk of HIV infection by 78% compared with unprotected anal intercourse (Reference 49). Furthermore, other methods to prevent HIV transmission have been explored, including male circumcision, vaccines, and microbicides. Male circumcision is associated with reduced transmission of sexually transmitted diseases, including HIV. Three large randomized controlled trials evaluated the impact of voluntary adult circumcision on HIV transmission rates in Kenya, South Africa, and Uganda. These trials showed a 50% to 60% reduction in the incidence of HIV infection for circumcised men compared with uncircumcised men (References 50–52). Another clinical trial in Uganda evaluated male-to-female HIV transmission rates when the males were circumcised and had viral loads less than 50,000 copies/mL, showing a significantly lower rate of transmission in this group compared with the uncircumcised group (Reference 53).

An effective HIV vaccine has yet to be found, despite decades of continuous research. At least two trials failed to show a protective benefit of vaccination (References 54, 55). However, a more recent study conducted in a community province in Thailand found a moderate protective effect for those who received the ALVAC/AIDSVAX vaccine regimen compared with those on placebo (Reference 56). Obstacles that make it so difficult to find a successful HIV vaccine are the virus's great genetic diversity, its ability to evade adaptive immune responses, its inability to induce a broadly reactive antibody response, and the establishment of latent reservoirs early in infection.

Recently, two promising clinical trials reported some benefits in the role of microbicides for preventing HIV transmission in adults. The first study (CAPRISA) found that a 1% tenofovir vaginal gel was associated with at least a 40% significantly reduced risk of transmission of HIV infection compared with placebo at 24 months (Reference 57). Another study was performed in transgender women and MSM using a preexposure prophylaxis oral regimen of daily tenofovir/emtricitabine compared with placebo. Those who received daily tenofovir/emtricitabine had a 44% relative risk reduction for HIV infection (Reference 58). With the exception of MTCT, no data exist on preventing HIV transmission with microbicides in children.

Pharmacologic Therapy

Since the development of the first ARVs in the late 1980s, treatment of pediatric HIV infection has evolved tremendously, especially with the arrival of the first PI. Use of combination antiretroviral therapy (cART) has improved survival, decreased the development and risk of OIs, improved growth and neurocognitive function, and enhanced the quality of life for HIV-infected children. Treatment of pediatric HIV infection, however, is very complex and should be tailored as well as possible to the patient's individual circumstances (Table 3) (References 28, 29). Moreover, it is worth emphasizing that the monthly average wholesale price of ARVs is very expensive (ranging from $361 to $3248 depending on the choice of ARV) (Reference 29). Annual costs of cART may range from $25,000 to $35,000; the monthly average wholesale price of NRTIs and NNRTIs tends to be considerably less than PIs and newer ARVs such as raltegravir, maraviroc, etravirine, and rilpivirine. These average wholesale price costs, which are derived from January 2012 data, may not represent the pharmacy acquisition costs or price paid by consumers (Reference 29). Affordability of cART may be considerably improved by insurance coverage as well as financial assistance programs such as AIDS drug assistance programs (ADAPs) and Ryan White funding. Because very few randomized clinical trials have been conducted in children, most of the ARVs indicated for treatment of pediatric HIV infection derive their approval from efficacy data in adults, pharmacokinetic and safety data from phase I/II trials of children, and nonrandomized open-label studies. Furthermore, very few phase III trials compare the effects of different ARV regimens in HIV-infected children.

The decision about when to start treatment is debatable because there are both advantages and disadvantages to initiating ARV therapy earlier when the patient is asymptomatic versus delaying treatment until the patient becomes symptomatic. Advantages of initiating ARV therapy early include having control of viral replication, allowing a lower viral load set point, reducing mutant viral strains, preserving immune function, preventing HIV disease progression, preventing sexual transmission of HIV, and preventing non-AIDS malignancies and other complications. However, delaying ARV therapy may also have some advantages such as reduced development of drug-resistant virus (because

Table 3. Factors to Consider When Choosing ARV Therapy for HIV-Infected Children (References 28, 29)

Factors for Consideration	Comments
Age of child	Different levels of caregiver involvement
Severity of disease	Virologic, immunologic, and clinical status
Affordability of ARVs	Annual costs of ARVs are very expensive (insurance coverage, ADAP, etc., can help offset costs)
Availability of appropriate dosage formulations	Liquid formulations including palatability Crushable/chewable tablets
Availability of relevant PK data for different age groups	Limited PK data available in the pediatric and adolescent HIV-infected populations
Potency of ARV regimen	Use three fully active drugs if possible.
Complexity of ARV regimen	Pill burden Dosing frequency Administration conditions (e.g., food considerations) Medication storage conditions (e.g., refrigeration) Expiration dates
Toxicity of ARV regimen	Adverse effect minimization and management
Preservation of future ARV treatment options	Maintain virologic control to avoid development of drug resistance/cross-resistance to other ARVs.
ARV treatment history	Potential for cross-resistance to other ARVs and previous intolerance of specific ARVs
Presence of ARV drug-resistant virus	Knowledge of previous resistance tests including genotypes and phenotypes is useful for determining appropriate ARV regimen (though complexity of regimen may be increased).
Presence of comorbid conditions	Potential for drug-drug or drug-disease interactions, including overlapping toxicities of drugs
Potential drug-drug interactions	Dose adjustments may be necessary with some medications; however, some ARVs may need to be avoided if contraindications exist.
Adherence potential	Critical for determining choice of appropriate ARV therapy (a good support system can benefit a patient greatly)

ADAP= AIDS drug assistance programs; ARV=antiretroviral; PK = pharmacokinetic.

of no drug-selective pressure), improved adherence to ARV regimen because the patient is symptomatic, and reduced or delayed adverse effects of ARV therapy. Of importance, $CD4^+$ cell count and viral load show considerable variability by age in children. Although these surrogate markers are poorly predictive of mortality and disease progression in infants, it is recommended to start treatment for all infants with a diagnosis of HIV infection because they are at greatest risk of rapid disease progression. Studies have shown that infants who receive early treatment have a significantly reduced risk of disease progression and achieve greater $CD4^+$ cell recovery compared with those who receive no ARV treatment (References 59–61). In the HIV Pediatric Prognostic Markers Collaborative Study meta-analysis, both $CD4^+$ percentage and HIV viral load were independent predictors of the risk of clinical progression or death in children older than 12 months (Reference 62). Furthermore, $CD4^+$ cell count is associated with risk of progression in children 5 years and older, similar to young adults. Therefore, recommendations for starting treatment for HIV-infected children between 1 and 4 years of age are based on $CD4^+$ percentage and, for those 5 years and older, on $CD4^+$ cell count. See Figure 1 for a summary of criteria and recommendations for when to initiate ARV therapy in HIV-infected children.

When initiating ARV therapy in treatment-naive HIV-infected children, the general approach is to use cART with at least three active ARV drugs from two different classes. Combination therapy is important because ARV resistance can develop more easily with monotherapy or dual therapy. The choice of initial cART for treatment-naive HIV-infected children is critically important because the selection of the first regimen can affect the consideration of future treatment options. Before starting treatment, adherence barriers to ARV therapy should be fully assessed and discussed with both the caregiver and patient. If possible, identifying potential problems and resolving them before starting ARV therapy are ideal. Adherence to ARVs is the cornerstone for achieving the goals of therapy because poor adherence to ARVs can lead to subtherapeutic levels, which increases the risk of developing ARV resistance and virologic failure.

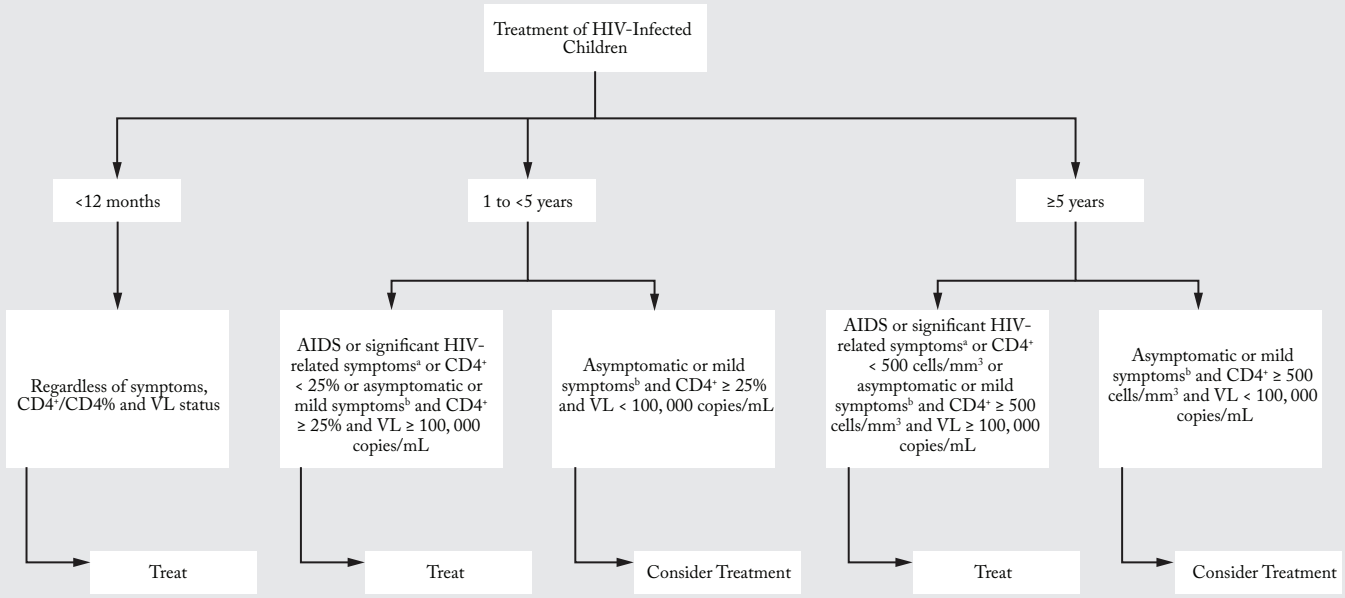


Figure 1. Summary of criteria and recommendations for when to initiate ARV therapy in HIV-infected children (Reference 28).

[a]CDC clinical categories C and B (except for category B condition single episode of serious bacterial infection).
[b]CDC clinical category A or N or the following category B condition single episode of serious bacterial infection.
AIDS = acquired immunodeficiency syndrome; ARV = antiretroviral; CDC = Centers for Disease Control; HIV = human immunodeficiency virus; VL = viral load.

To date, more than 20 ARV drugs are approved for use in the treatment of HIV, of which 17 have an approved pediatric treatment indication. Currently, there are five ARV classes: NRTIs, NNRTIs, PIs, entry inhibitors (including fusion inhibitors and attachment inhibitors such as CCR5 antagonists), and integrase strand transfer inhibitors. See the Pathophysiology section for more information on the pharmacology of antiretrovirals. Common ARV combinations for treatment-naive pediatric HIV infection include two NRTIs plus one NNRTI, or two NRTIs plus one PI with or without ritonavir. Although monotherapy for treatment of HIV infection is not recommended because of the potential for resistance development, one exception is zidovudine monotherapy for 6 weeks in infants of indeterminate HIV status to prevent perinatal HIV transmission. Should infants have a confirmation of HIV infection while receiving zidovudine monotherapy, zidovudine should be discontinued, and combination therapy with three active ARVs should be used for treatment (this may include zidovudine, if genotype shows no resistance). Antiretroviral drug resistance testing is always recommended before initiating therapy in treatment-naive HIV-infected children because it is possible for infants to acquire drug resistance from their HIV-infected mothers. For example, infants given single-dose peripartum nevirapine for prevention of transmission should not use nevirapine as combination therapy, should they later be given a diagnosis of HIV infection, because this maternal-infant prophylaxis could be associated with resistance to nevirapine and subsequent virologic failure (Reference 63). Drug-resistant virus has been detected in 6% to 16% of ARV-naive adults and in 18% of adolescents with recent infection in both the United States and Europe (References 64–68).

Recommendations for optimal ARV therapy among pediatric patients are continuously updated as new drug formulations are developed and more information regarding efficacy and safety becomes available. The U.S. Department of Health and Human Services guidelines are written by a panel of experts who assimilate the clinical trials of adult and pediatric patients to date (References 28, 29). Their recommendations for specific ARV drugs or regimens are stratified into three different categories for treatment-naive HIV-infected pediatric patients: preferred, alternative, or for use in special circumstances (Reference 28). Updates to these guidelines can be found at www.aidsinfo.nih.gov. Some primary factors that may affect their recommendations for ARV use can be found in Table 3. See Table 4 for a summary of various ARVs used to treat HIV infection, including dosing formulations, dosing, special instructions, and metabolism/mode of clearance for each ARV.

Table 4. Summary of ARVs

Generic (Brand, Abbreviation)	Dosage Formulation	Dosing	Special Instructions	Mode of Clearance/ Metabolism	Adverse Effects	Management/Monitoring
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
Abacavir (Ziagen, ABC)	**Pediatric oral solution:** 20 mg/mL **Tablets:** 300 mg (scored)	**≥ 3 months:** (Oral solution) 8 mg/kg BID (max 300 mg BID) and 16 mg/kg QD (max 600 mg QD for patients who have undetectable viral load and stable $CD4^+$ cell counts) Scored 300-mg tablet (Wt ≥ 14 kg) **Adolescent (≥ 16 years)/Adults:** 300 mg BID or 600 mg QD Trizivir (abacavir/lamivudine/zidovudine) 1 tablet BID (≥ 40 kg) Epzicom (abacavir/lamivudine) 1 tablet QD	• With or without food • Alcohol may increase ABC concentrations.	Extensively metabolized by alcohol dehydrogenase and glucuronyl transferase—only a small % excreted unchanged	• Hypersensitivity reaction (symptoms may include fever, rash, malaise or fatigue, and shortness of breath)	• Screen for *HLA-B*5701* (if positive, do not use ABC and ABC allergy should be noted in medical record). • If hypersensitivity reaction is suspected, ABC should be discontinued immediately. • Do not rechallenge if experienced previous hypersensitivity reaction. • Dose adjust in hepatic failure.
Didanosine (Videx, ddI)	**Oral solution:** 10 mg/mL **Videx EC delayed-release capsules:** 125 mg, 200 mg, 250 mg, 400 mg	**2 weeks to < 3 months:** 50 mg/m² of BSA BID **> 3–8 months:** 100 mg/m² of BSA BID **Oral solution (> 8 months):** 120 mg/m² of BSA BID (Dose range: 90–150 mg/m² of BSA BID, max dose 200 mg BID) **Videx EC (6–18 years and ≥ 20 kg):** **In treatment-naive individuals 3–21 years of age:** 240 mg/m² BSA QD (oral solution or capsules) has been used with good viral suppression. **Adolescent/Adult dose:** < 60 kg: 250 mg QD ≥ 60 kg: 400 mg QD	• Administer ddI on an empty stomach (30 minutes before or 2 hours after a meal). • Shake oral solution well. Keep refrigerated; admixture is stable for 30 days.	Renal	• Peripheral neuropathy • Pancreatitis (dose related and less common in children than in adults) • Retinal changes (optic neuritis) • Noncirrhotic portal hypertension (rare) • Diarrhea, abdominal pain, nausea, and vomiting • Lactic acidosis and severe hepatomegaly with steatosis (increased risk when used with d4T) • Insulin resistance/diabetes mellitus	• LFTs • Pancreatic enzymes lipase and amylase • Blood glucose • Dose adjust in renal failure.

Scored 300-mg tablet (Wt ≥ 14 kg)

Wt (kg)	Morning Dose (tablet; mg)	Evening Dose (tablet; mg)
14–21	150	150
> 21 to < 30	150	300
≥ 30	300	300

Videx EC (6–18 years and ≥ 20 kg):

Wt (kg)	Dose (mg QD)
20 to < 25	200
25 to < 60	250
≥ 60	400

<table>
<tr>
<td>Emtricitabine (Emtriva, FTC)</td>
<td>Oral solution: 10 mg/mL

Capsules: 200 mg</td>
<td>0–3 months:
(Oral solution) 3 mg/kg QD

3 months to 17 years:
(Oral solution) 6 mg/kg QD (max 240 mg QD) or
(Capsules) (> 33 kg) 200 mg QD

Adolescent (≥ 18 years)/Adult dose:
Oral solution: 240 mg (24 mL) QD
Capsules: 200 mg QD
Truvada (tenofovir/emtricitabine) 1 tablet QD
Atripla (tenofovir/emtricitabine/efavirenz) 1 tablet QD
Complera (tenofovir/emtricitabine/rilpivirine) 1 tablet QD</td>
<td>• With or without food
• Oral solution can be kept at RT if used within 3 months; refrigerate if long-term storage is used.</td>
<td>Renal</td>
<td>• Minimal toxicity
• Nausea, diarrhea
• Hyper-pigmentation/skin discoloration on palms and/or soles (mostly in nonwhite patients)</td>
<td>• Screen patients for hepatitis B virus before use of FTC. Severe acute exacerbation of hepatitis can occur when FTC is discontinued (monitor LFTs for several months after therapy with FTC is discontinued).
• Dose adjust in renal failure.</td>
</tr>
<tr>
<td>Lamivudine (Epivir, 3TC)</td>
<td>Oral solution: 10 mg/mL

Tablets: 150 mg (scored), 300 mg</td>
<td>< 4 weeks for prevention of transmission or treatment:
2 mg/kg BID

> 4 weeks:
4 mg/kg (up to 150 mg) BID

Dosing for scored 150-mg tablet (wt ≥ 14 kg):
<table>
<tr><th>Wt (kg)</th><th>Morning dose (mg)</th><th>Evening dose (mg)</th></tr>
<tr><td>14–21</td><td>75</td><td>75</td></tr>
<tr><td>> 21–< 30</td><td>75</td><td>150</td></tr>
<tr><td>≥ 30</td><td>150</td><td>150</td></tr>
</table>
≥ 16 years:
Body weight ≥ 50 kg: 150 mg BID or 300 mg QD

Body weight < 50 kg: 4 mg/kg (up to 150 mg) BID

Trizivir (abacavir/lamivudine/zidovudine) 1 tablet BID (≥ 40 kg)
Epzicom (abacavir/lamivudine) 1 tablet QD
Combivir (lamivudine/zidovudine) 1 tablet BID (≥ 30 kg)</td>
<td>• With or without food
• Store oral solution at RT.</td>
<td>Renal</td>
<td>• Minimal toxicity
• Headache
• Nausea
• Pancreatitis</td>
<td>• Pancreatic enzymes lipase and amylase
• Screen patients for hepatitis B virus before use of 3TC. Severe acute exacerbation of hepatitis can occur when 3TC is discontinued (monitor LFTs for several months after therapy with 3TC is discontinued)
• Dose adjust in renal failure.</td>
</tr>
</table>

(continued)

Table 4. Summary of ARVs *(continued)*

Generic (Brand, Abbreviation)	Dosage Formulation	Dosing	Special Instructions	Mode of Clearance/ Metabolism	Adverse Effects	Management/Monitoring
Stavudine (Zerit, d4T)	**Oral solution:** 1 mg/mL **Capsules:** 15 mg, 20 mg, 30 mg, 40 mg	**Birth to 13 days:** 0.5 mg/kg BID **14 days and up to 30 kg:** 1 mg/kg BID **Adolescent (≥ 30 kg)/Adult dose:** 30 to < 60 kg: 30 mg BID ≥ 60 kg: 40 mg BID	• With or without food • Shake oral solution well; keep refrigerated; will remain stable for 30 days	Renal	• Peripheral neuropathy • Pancreatitis • Lipodystrophy • Lactic acidosis with hepatic steatosis (higher incidence than with other NRTIs) • Hyperlipidemia • Rapidly progressive ascending neuromuscular weakness (rare) • Insulin resistance/diabetes mellitus	• LFTs • Pancreatic enzymes lipase and amylase • Lipids (especially triglycerides) • Blood glucose • Dose adjust in renal failure.
Tenofovir disoproxil fumarate (Viread, TDF)	**Oral powder:** 40 mg/g **Tablets:** 150 mg, 200 mg, 250 mg, 300 mg	**Pediatric (≥ 2 years and < 12 years):** 8 mg/kg up to maximum of 300 mg QD using oral powder or tablets **Pediatric (≥ 2 years) dose, oral powder:** Wt (kg) / Dose (scoops of powder* QD) 10 to < 12 — 2 12 to < 14 — 2.5 14 to < 17 — 3 17 to < 19 — 3.5 19 to < 22 — 4 22 to < 24 — 4.5 24 to < 27 — 5 27 to < 29 — 5.5 29 to < 32 — 6 32 to < 34 — 6.5 34 to < 35 — 7 ≥ 35 — 7.5 *One level scoop contains 40 mg of tenofovir in 1g of powder **Pediatric (≥ 2 years and ≥ 17 kg) dose, tablets:** Wt (kg) / Dose (mg QD) 17 to < 22 — 150 22 to < 28 — 200 28 to < 35 — 250 ≥ 35 — 300 **Adolescent (≥ 12 years and > 35 kg) dose:** 300 mg QD **Adult dose:** 300 mg QD Truvada (tenofovir/emtricitabine) 1 tablet QD Atripla (tenofovir/emtricitabine/efavirenz) 1 tablet QD Complera (tenofovir/emtricitabine/rilpivirine) 1 tablet QD	• With or without food (for tablets only) • Mix oral powder in a container with 2–4 oz of soft food (e.g., yogurt, applesauce, baby food) and ingest entire mixture immediately to avoid bitter taste. • Do not administer oral powder in liquid form. • Absorption is enhanced when administered with a high-fat meal.	Renal	• Diarrhea, nausea, vomiting, flatulence • Renal insufficiency, Fanconi syndrome • Decreased bone mineral density, osteomalacia	• DXA scan before initiating TDF and 6 months later, especially in prepubertal patients and those in early puberty (Tanner stages 1 and 2) • Serum creatinine/BUN • Urinalysis (proteinuria/glycosuria) • Decreased serum phosphate • Screen patients for hepatitis B virus before use of TDF. Severe acute exacerbation of hepatitis can occur when TDF is discontinued (monitor LFTs for several months after therapy with TDF is discontinued). • Dose adjust in renal failure.

<table>
<tr>
<td>Zidovudine (Retrovir, AZT or ZDV)</td>
<td>Syrup:
10 mg/mL

Concentrate for injection/ intravenous infusion:
10 mg/mL

Capsules:
100 mg

Tablets:
300 mg</td>
<td>Dose for infant younger than 35 weeks' gestation for prevention of transmission or treatment:
(IV) 1.5 mg/kg or
(Oral) 2 mg/kg BID, increased to 3 mg/kg BID at 2 weeks of age (neonates ≥ 30 weeks' gestational age) or at 4 weeks of age (neonates < 30 weeks' gestational age)

< 6 weeks for prevention of transmission or treatment:
(Oral) 2 mg/kg every 6 hours
(IV) 1.5 mg/kg every 6 hours

6 weeks to < 18 years:
BSA dosing:
(Oral) 180–240 mg/m^2 BID or 160 mg/m^2 TID

Wt-based dosing:
<table>
<tr><th>Wt (kg)</th><th>BID</th></tr>
<tr><td>4 to < 9</td><td>12 mg/kg</td></tr>
<tr><td>≥ 9 to < 30</td><td>9 mg/kg</td></tr>
<tr><td>≥ 30</td><td>300 mg</td></tr>
</table>
Adolescent (≥ 18 years)/Adult dose:
200 mg TID or 300 mg BID
Trizivir (abacavir/lamivudine/zidovudine) 1 tablet BID (≥ 40 kg)
Combivir (lamivudine/zidovudine) 1 tablet BID (≥ 30 kg)</td>
<td>• With or without food</td>
<td>Renal recovery of unchanged drug is less than 20%, extensive liver metabolism including glucuronide conjugates</td>
<td>• Macrocytic anemia
• Granulocytopenia
• Gastrointestinal intolerance
• Headache
• Fatigue
• Myopathy
• Lipodystrophy
• Lactic acidosis with hepatic steatosis
• Nail pigmentation
• Insulin resistance/diabetes mellitus
• Hyperlipidemia</td>
<td>• Discontinue AZT if severe granulocytopenia or anemia; use of erythropoietin 50–200 international units/kg/dose TIW, filgrastim 5–10 mcg/kg QD, or transfusion may be necessary
• If feasible, discontinue non-ARV marrow-toxic drugs.
• CBC
• LFTs
• Blood glucose
• Lipids
• Dose adjust in renal failure.
• May need to dose adjust in hepatic impairment</td>
</tr>
<tr>
<td colspan="6">Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)</td>
</tr>
<tr>
<td>Efavirenz (Sustiva, EFV)</td>
<td>Tablets:
600 mg

Capsules:
50 mg,
200 mg</td>
<td>> 3 years and > 10 kg:
<table>
<tr><th>Wt (kg)</th><th>QD (mg)</th></tr>
<tr><td>10 to < 15</td><td>200</td></tr>
<tr><td>15 to < 20</td><td>250</td></tr>
<tr><td>20 to < 25</td><td>300</td></tr>
<tr><td>25 to < 32.5</td><td>350</td></tr>
<tr><td>32.5 to < 40</td><td>400</td></tr>
<tr><td>≥ 40</td><td>600</td></tr>
</table>
Adolescent (≥ 40 kg)/Adult dose:
600 mg QD
Atripla (tenofovir/emtricitabine/efavirenz) 1 tablet QD</td>
<td>• Take on an empty stomach at bedtime.
• Avoid administration with high-fat meal because this may increase EFV concentrations.</td>
<td>•Hepatic
•CYP 3A4 and 2B6 inducer
•CYP3A4 and 2B6 substrate</td>
<td>• CNS adverse effects (may include insomnia, abnormal dreams, dizziness, somnolence)
• Rash
• Hepatotoxicity
• Teratogenic
• Potential lipohypertrophy</td>
<td>• EFV may cause false-positive cannabinoid and benzodiazepine tests.
• LFTs
• EFV should be avoided in first trimester of pregnancy (pregnancy category D).
• Lipids
• Use with caution in hepatic impairment.</td>
</tr>
</table>

(continued)

Table 4. Summary of ARVs *(continued)*

Generic (Brand, Abbreviation)	Dosage Formulation	Dosing	Special Instructions	Mode of Clearance/ Metabolism	Adverse Effects	Management/Monitoring
Etravirine (Intelence, ETR)	**Tablets:** 100 mg, 200 mg	**Adult dose (> 16 years and ARV experienced):** 200 mg BID **Investigational dosing for children 6–17 years:** 5.2 mg/kg (max 200 mg) BID (lower exposure of ETR seen in adolescents 12–17 years than in adults)	• Take after meals (AUC decreased by 50% on an empty stomach). • Store at RT in original container because of sensitivity to moisture. • Tablets can be dispersed in small amount of water to make slurry: once dispersed, stir well and consume immediately. Also, rinse glass with water a few times, swallowing each rinse to make sure entire dose is taken.	• Hepatic • CYP3A4 inducer • CYP 2C9 and 2C19 inhibitor • CYP3A4, 2C9 and 2C19 substrate	• Nausea • Diarrhea • Rash • Hypersensitivity reaction (including rash and hepatic failure)	• LFTs • History of NNRTI-related rash with EFV or NVP does not increase risk of developing rash with etravirine (however, etravirine should be avoided in patients with a history of severe rash with EFV and NVP). • No dosage adjustment in patients with mild-moderate hepatic impairment
Nevirapine (Viramune, NVP)	**Suspension:** 10 mg/mL **Tablets:** 200 mg, 400 mg XR	**< 14 days (when used for prophylaxis of mother-to-child transmission of HIV):** Single dose of 2 mg/kg (given to infants between birth and 72 hours after birth) **≥ 15 days and < 8 years:** 200 mg/m^2 of BSA (max dose 200 mg) BID **≥ 8 years:** 120–150 mg/m^2 of BSA (max dose 200 mg) BID **Adolescent/Adult dose:** 200 mg BID Initiate therapy with 200 mg given QD for the first 14 days; then increase to 200 mg BID if there is no rash or elevated LFT. No data exist for 400-mg XR tablet for patients < 18 years.	• With or without food • NVP is initiated at a lower dose and increased in a stepwise fashion because of autoinduction. • Shake suspension well and store at RT.	• Hepatic • 80% excreted in urine as glucuronidated metabolites • CYP3A and 2B6 inducer	• Rash • Hepatotoxicity	• If rash occurs during 14-day lead-in period, do not increase dose until rash resolves. • If NVP has been discontinued for > 7 days, reinitiate NVP with QD for 2 weeks, followed by full BID dosing. • Avoid starting NVP in females with CD4$^+$ > 250 and in males with CD4$^+$ > 400 cells/mm^3. • LFTs at baseline, 2 weeks, 4 weeks, and then every 3 months (if clinical hepatitis or hypersensitivity reactions occur, NVP should be permanently discontinued) • Use with caution in children having elevated pretreatment LFTs. • NVP should not be used in patients with moderate to severe hepatic impairment.

Rilpivirine (Edurant, RPV)	**Tablets:** 25 mg	**Adult dose and ARV naive:** 25 mg QD Complera (tenofovir/emtricitabine/rilpivirine) 1 tablet QD	• Take with a meal.	•Hepatic •CYP3A substrate	• CNS adverse effects (depression, mood changes, insomnia) are less common than with EFV. • Headache • Rash	• Use with caution when using with another drug that has known risk of torsade de pointes. • Use with caution in patients who have a viral load greater than 100,000 copies/mL because of increased risk of virologic failure. • No dosage adjustment in patients with mild-moderate hepatic impairment • Use with caution in patients with severe renal impairment or ESRD.
Protease Inhibitors (PIs)						
Atazanavir (Reyataz, ATV)	**Capsules:** 100 mg, 150 mg, 200 mg, 300 mg	**For children 6–18 years:** Treatment-naive children only* 15 to < 25 kg: ATV 150 mg + RTV 80 mg Treatment-naive and treatment-experienced children* 25 to < 32 kg: ATV 200 mg + RTV 100 mg 32 to < 39 kg: ATV 250 mg + RTV 100 mg ATV ≥ 39 kg: ATV 300 mg + RTV 100 mg *Take ATV/RTV QD with food. **Adolescent (≥ 18–21)/Adult dose**: *Treatment naive*: ATV 300 mg + RTV 100 mg or ATV 400 mg QD with food *Treatment experienced*: ATV 300 mg + RTV 100 mg QD with food **With EFV (only in treatment naive):** ATV 400 mg + RTV 100 mg + EFV 600 mg QD **With TDF:** Always use ATV 300 mg + RTV 100 mg + TDF 300 mg QD with food because TDF can decrease ATV exposure	• Take with food to improve absorption of ATV. • Separate ATV dosing from acid-suppressive therapy (antacids should be separated by 1–2 hours; histamine-2 blockers should be separated by 12 hours) (if TDF is also used, use ATV 400 mg + RTV 100 mg QD); proton pump inhibitors (≤ 20 mg equivalent dosing of omeprazole) should be separated by 12 hours from boosted ATV). • Proton pump inhibitors not recommended in treatment-experienced patients taking ATV.	•Hepatic •CYP3A4 and UGT1A1 inhibitor •CYP3A4 substrate	• Indirect hyperbilirubinemia (sclera icterus) • Nephrolithiasis (rare) • Rash	• Hyperbilirubinemia may resolve with time (may discontinue if cosmetically unappealing). • Total bilirubin • Urinalysis • Dose adjust in hepatic failure (should not be given to patients with severe hepatic impairment). • Treatment-experienced patients with ESRD on hemodialysis should not use ATV.

(continued)

Table 4. Summary of ARVs *(continued)*

<table>
<tr><th>Generic (Brand, Abbreviation)</th><th>Dosage Formulation</th><th>Dosing</th><th>Special Instructions</th><th>Mode of Clearance/ Metabolism</th><th>Adverse Effects</th><th>Management/Monitoring</th></tr>
<tr>
<td>Darunavir (Prezista, DRV)</td>
<td>Suspension:
100 mg/mL

Tablets:
75 mg,
150 mg,
400 mg,
600 mg</td>
<td>Pediatric dosing (> 3–18 years and > 10 and < 15 kg), DRV oral suspension/ RTV oral solution:
<table>
<tr><td>Wt (kg)</td><td>BID (DRV mg/RTV mg)</td></tr>
<tr><td>10 to < 11</td><td>200 (2 mL)/32 (0.4 mL)</td></tr>
<tr><td>11 to < 12</td><td>220 (2.2 mL)/32 (0.4 mL)</td></tr>
<tr><td>12 to < 13</td><td>240 (2.4 mL)/40 (0.5 mL)</td></tr>
<tr><td>13 to < 14</td><td>260 (2.6 mL)/40 (0.5 mL)</td></tr>
<tr><td>14 to < 15</td><td>280 (2.8 mL)/48 (0.6 mL)</td></tr>
</table>
RTV oral solution: 80 mg/mL

Pediatric dosing (> 3–18 years and ≥ 15 kg and unable to swallow tablets), DRV oral suspension/RTV oral solution:
<table>
<tr><td>Wt (kg)</td><td>BID (DRV mg/RTV mg)</td></tr>
<tr><td>15 to < 30</td><td>375* (3.8 mL)/50 (0.6 mL)</td></tr>
<tr><td>30 to < 40</td><td>450* (4.6 mL)/60 (0.75 mL)</td></tr>
<tr><td>≥ 40</td><td>600 (6 mL)/100 (1.25 mL)</td></tr>
</table>
*Doses rounded off.
RTV oral solution: 80 mg/mL

Pediatric dosing (> 3–18 years and ≥ 15 kg and able to swallow tablets), DRV tablets/RTV oral solution or tablets/capsules:
<table>
<tr><td>Wt (kg)</td><td>BID (DRV mg/RTV mg)</td></tr>
<tr><td>15 to < 30</td><td>375/50* (0.6 mL)</td></tr>
<tr><td>30 to < 40</td><td>450/60* (0.75 mL)</td></tr>
<tr><td>≥ 40</td><td>600/100* (1.25 mL) or 1 tablet/capsule</td></tr>
</table>
*RTV oral solution: 80 mg/mL
RTV tablets/capsules: 100 mg

Adult dose (≥ 18 years): Treatment naive:
DRV 800 mg + RTV 100 mg both QD
Treatment experienced with at least one DRV mutation:
DRV 600 mg BID + RTV 100 mg BID</td>
<td>• Take with food.
• Because DRV has a sulfa moiety, use caution in patients with sulfonamide allergy.
• Store at RT.</td>
<td>•Hepatic
•CYP3A4 substrate and inhibitor</td>
<td>• Rash
• Hepatotoxicity
• Headaches</td>
<td>• LFTs
• Use caution in patients with hepatic impairment (do not use in those with severe hepatic impairment).</td>
</tr>
</table>

Fosamprenavir (Lexiva, FPV)	**Suspension:** 50 mg/mL **Tablets:** 700 mg	**Treatment naive (2–5 years):** Unboosted FPV 30 mg/kg (max 1400 mg) BID **Treatment naive (≥ 6–18 years):** Unboosted FPV 30 mg/kg (max 1400 mg) BID or boosted FPV 18 mg/kg (max 700 mg) + RTV 3 mg/kg (max 100 mg) both BID **Treatment experienced (≥ 6–18 years):** Boosted FPV 18 mg/kg (max 700 mg) + RTV 3 mg/kg (max 100 mg) both BID **Adult dosing with FPV tablets:** ≥ 47 kg → 1400 mg BID ≥ 39 kg → 700 mg + RTV 100 mg BID **Adolescents (> 18 years)/Adult dose:** *Treatment naive:* FPV 1400 mg BID FPV 700 mg + RTV 100 mg BID FPV 1400 mg + RTV 100–200 mg QD *Treatment experienced*: FPV 700 mg + RTV 100 mg BID **Dosing of FPV with EFV (adults):** FPV 700 mg + RTV 100 mg BID + EFV 600 mg QD or FPV 1400 mg + RTV 300 mg + EFV 600 mg QD (PI-naive patients)	• With food • Because FPV has a sulfa moiety, use caution in patients with sulfonamide allergy. • Shake oral suspension well before use (refrigeration not required).	•Hepatic •FPV is a prodrug and is hydrolyzed to amprenavir (APV). •APV is a CYP3A4 inhibitor, inducer, and substrate.	• Rash • Vomiting • Headache • Nephrolithiasis • Perioral paresthesias	• Urinalysis • Dose adjust in hepatic impairment.
Indinavir (Crixivan, IDV)	**Capsules:** 100 mg, 200 mg, 400 mg	**Adolescent/Adult dose:** 800 mg TID or 800 mg IDV + 100 mg or 200 mg RTV BID	• IDV without RTV should be administered on an empty stomach. • Adequate hydration is necessary to minimize nephrolithiasis (≥ 48 oz of daily fluid in adults). • Store at RT in original container with desiccant because capsules are sensitive to moisture.	•Hepatic •CYP3A4 substrate and inhibitor	• Nephrolithiasis • Hepatitis • Indirect hyperbilirubinemia (sclera icterus) • Headache • Metallic taste • Thrombocytopenia • Hemolytic anemia	• Hyperbilirubinemia may resolve with time (may discontinue if cosmetically unappealing). • Total bilirubin • Urinalysis • CBC • LFTs • Dose adjust in hepatic failure.

(continued)

Table 4. Summary of ARVs *(continued)*

<table>
<tr><th>Generic (Brand, Abbreviation)</th><th>Dosage Formulation</th><th>Dosing</th><th>Special Instructions</th><th>Mode of Clearance/ Metabolism</th><th>Adverse Effects</th><th>Management/Monitoring</th></tr>
<tr><td>Lopinavir/ ritonavir (Kaletra, LPV/ RTV)</td><td>Solution:
80 mg/
20 mg/mL

Tablets: 100/25 mg, 200/50 mg</td><td>Third-trimester dosing:
LPV/r 600/150 mg BID

14 days to 12 months:
Oral solution → 300 mg/75 mg/m^2 BSA or 16 mg/4 mg/kg BID

> 12 months to 18 years:
BSA dosing: 230/57.5 mg of LPV/r per m^2 BID (for patients already taking LPV/r, immediate dose reduction at age 12 months is not recommended)

Wt-based dosing:
< 15 kg: 12/3 mg of LPV/r per kg BID
≥ 15–40 kg: 10/2.5 mg of LPV/r per kg BID
≥ 40 kg: 400 mg/100 mg of LPV/r BID

<table><tr><td colspan="3">Dosing for 100 mg/25 mg LPV/r tablets</td></tr><tr><td>Wt (kg)</td><td>BSA m^2</td><td>No. of Tablets BID</td></tr><tr><td>15–25</td><td>≥ 0.6 to < 0.9</td><td>2</td></tr><tr><td>> 25–35</td><td>≥ 0.9 to < 1.4</td><td>3</td></tr><tr><td>> 35</td><td>≥ 1.4</td><td>4 or 2 of the 200/50-mg adult tablets</td></tr></table>
Adult (> 18 years) dose:
800 mg/200 mg LPV/r QD or
400 mg/100 mg LPV/r BID (especially in patients with ≥ 3 LPV mutations)

Patients ≥ 12 months of age and also receiving EFV, NVP, FPV, or NFV require higher than standard dosing of LPV/r.</td><td>• Take tablets with or without food.
• Solution should be refrigerated (expires after 60 days at RT).
• Oral solution contains 42.4% alcohol by volume.
• Oral solution should be administered with food for enhanced absorption.</td><td>• Hepatic
• CYP3A4 substrate and inhibitor</td><td>• Diarrhea
• QT prolongation and torsade de pointes
• Postmarketing adverse effects of cardiac toxicity (complete AV block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, depression and respiratory problems have been reported in preterm neonates
• Asthenia
• Taste alteration</td><td>• Electrocardiogram
• Can be used in children 42 weeks' postmenstrual age and older and a postnatal age of 14 days.
• Use caution in patients with hepatic impairment.</td></tr>
<tr><td>Nelfinavir (Viracept, NFV)</td><td>Powder for oral suspension:
50 mg of powder per gram

Tablets:
250 mg,
625 mg</td><td>2–13 years:
44–55 mg/kg BID or 25–35 mg/kg TID

Adolescent/adult dose:
1250 mg BID or 750 mg TID</td><td>• Take with food.
• Tablets can be dissolved in a small amount of water to make slurry.
• Tablets can also be crushed and administered with pudding.
• When reconstituted, oral suspension is stable for 6 hours when refrigerated.
• Mixing powder with acidic food or juice may result in poor taste.</td><td>• Hepatic
• CYP 2C19 and CYP3A4 substrate
• Metabolized to active metabolite M8
• CYP3A inhibitor</td><td>• Diarrhea
• Abdominal pain
• Asthenia</td><td>• Do not use in patients with moderate to severe hepatic impairment.</td></tr>
</table>

Ritonavir (Norvir, RTV)	**Oral solution:** 80 mg/mL (contains 43% alcohol by volume) **Capsules:** 100 mg **Tablets:** 100 mg	• RTV is used as a pharmacokinetic booster (increases concentrations of coadministered PIs). • Dosing of RTV varies with different PIs (see individual PIs to determine dosing of RTV).	• May take with food to minimize gastrointestinal intolerance and improve absorption • Refrigerate capsules if not used within 30 days. • Tablets need not be refrigerated. • Store oral solution at RT (must not be refrigerated); shake well before use. • Use oral solution within 6 months.	•Hepatic •CYP3A4 and CYP2D6 inhibitor	• Circumoral paresthesias • Hypertriglyceridemia • Taste perversion • Hepatitis	• Lipids • LFTs • Use caution when using RTV in patients with moderate to severe hepatic impairment.
Saquinavir (Invirase, SQV)	**Hard gel capsules:** 200 mg **Tablets:** 500 mg	**Investigational dosing for treatment-experienced children (≥ 2 years based on limited data):** Wt (kg) / Dosing (BID) 5 to < 15 / SQV 50 mg/kg + RTV 3 mg/kg 15–40 / SQV 50 mg/kg + RTV 2.5 mg/kg ≥ 40 / SQV 50 mg/kg + RTV 100 mg SQV may be coadministered with LPV/r in patients ≥ 7 years for salvage therapy. **Adolescent (≥ 16 years)/Adult dose:** **SQV 1000 mg + RTV 100 mg BID**	• Take within 2 hours after food to improve absorption. • Always take with RTV (never unboosted because of poor bioavailability). • May cause photosensitivity reactions if exposed to sun; recommend protective clothing or sunscreen use	•Hepatic •CYP3A4 substrate and inhibitor	• Headache • Abdominal discomfort • QT prolongation and torsades de pointes • Photosensitivity	• An electrocardiogram is recommended before initiation of SQV (patients with baseline QT intervals greater than 450 milliseconds should not receive SQV). • SQV is also not recommended in patients who are taking other drugs that can cause QT prolongation. • Use caution in patients with mild to moderate hepatic impairment. • Contraindicated in patients with severe hepatic impairment
Tipranavir (Aptivus, TPV)	**Oral solution:** 100 mg/mL **Capsules:** 250 mg	**2–18 years:** BSA dosing → 375 mg/m^2 + RTV 150 mg/m^2 BID or Wt-based dosing → 14 mg/kg + RTV 6 mg/kg [maximum TPV 500 mg + RTV 200 mg BID] **Adult dose:** TPV 500 mg + RTV 200 mg BID	• Take with food. • Oral solution contains 116 international units of vitamin E per milliliter. • Because TPV has a sulfa moiety, use caution in patients with sulfonamide allergy. • Store oral solution at RT; do not refrigerate or freeze. • Once oral solution is opened, it must be used within 60 days. • Capsules can be kept at RT if used within 60 days; refrigerate capsules if longer storage is anticipated.	•Hepatic •CYP3A4 substrate and inducer	• Rash • Hepatotoxicity • Intracranial hemorrhage (rare) • Hypertriglyceridemia	• LFTs • Use caution in patients at risk of increased bleeding from surgery, trauma, or other medical conditions or receiving drugs such as antiplatelets, anticoagulants, or excessive vitamin E supplemental doses. • Lipids (especially triglycerides) • Contraindicated in patients with moderate or severe hepatic impairment

(continued)

Table 4. Summary of ARVs *(continued)*

Generic (Brand, Abbreviation)	Dosage Formulation	Dosing	Special Instructions	Mode of Clearance/ Metabolism	Adverse Effects	Management/Monitoring
Entry Inhibitors						
Enfuvirtide, (Fuzeon, ENF or T-20)	**Lyophilized powder for injection:** 108-mg vial reconstituted with 1.1 mL of sterile water will make 90 mg/mL.	**6–16 years:** 2 mg/kg SC BID Maximum dose is 90 mg (1 mL) BID. **Adolescents (> 16 years)/Adult dose:** 90 mg (1 mL) SC BID	• Inject subcutaneously into the upper arm, anterior thigh, or abdomen. • Allow up to 45 minutes for reconstituted powder to dissolve completely in solution; do not shake. • Once reconstituted, inject immediately or keep refrigerated until use. • Reconstituted vial must be used within 24 hours.	• Catabolism to constituent individual amino acids	• Injection site reactions • Bacterial pneumonia and local site cellulitis • Hypersensitivity reaction	• Rotate injection sites to minimize reactions. • Local reactions may also be minimized by applying heat or ice after injection; alternatively, may gently massage the injection site to better disperse the dose • Discontinue if signs and symptoms of hypersensitivity reaction are suspected; seek medical attention immediately.
Maraviroc (Selzentry, MVC)	**Tablets:** 150 mg, 300 mg	**Adolescent (> 16 years)/Adult dose:** When given with potent CYP3A inhibitors (with or without CYP3A inducers); exception TPV: 150 mg BID When given with ENF, NRTIs, RAL, NVP, TPV/r, and no other CYP3A inhibitors or inducers: 300 mg BID When given with potent CYP3A inducers such as EFV and ETR (without strong CYP3A inhibitor): 600 mg BID	• Use CCR5 tropism assay to determine the feasibility of ARVs. • Take with or without food.	• Hepatic • CYP3A4 substrate	• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Fever • Rash • Upper respiratory tract infections • Hepatotoxicity • Orthostatic hypotension	• LFTs • Blood pressure if taking other antihypertensive drugs • Use caution in patients with underlying cardiac disease. • Use caution in patients with hepatic impairment. • Do not use MVC in patients with creatinine clearance < 30 mL/ minute who are also taking other drugs that are potent CYP3A4 inhibitors or inducers.
Integrase Inhibitor						
Raltegravir (Isentress, RAL)	**Chewable tablets:** 25 mg, 100 mg (scored) **Film-coated tablets:** 400 mg	**Pediatric dose:** **2 to < 6 years, > 10 kg: Chewable tablets** Wt (kg) / BID (mg): 10 to < 14 / 75; 14 to < 20 / 100; 20 to < 28 / 150; 28 to < 40 / 200; ≥ 40 / 300 **6 to < 12 years:** < 25 kg, chewable tablets: Weight based to maximum of 300 mg BID (as specified in table above) **> 25 kg, chewable tablets**: Weight based to maximum of 300 mg BID (as specified in table above) **> 25 kg, film-coated tablets: 400 mg BID** **Adolescent (≥ 12 years)/Adult dose:** 400 mg BID	• Take with or without food. • Chewable tablets may be chewed or swallowed whole. • Chewable tablet and film-coated tablet are not bioequivalent (do not substitute chewable tablets for the film-coated tablet).	• UGT1A1 glucuronidation • UGT1A1 inhibitors such as ATV may increase RAL concentrations. • UGT1A1 inducers such as TPV and rifampin may decrease RAL concentrations.	• Headache • Nausea • Diarrhea • Muscle weakness and rhabdomyolysis	• Creatinine phosphokinase • No dosage adjustment in patients with renal impairment or mild to moderate hepatic impairment (no data available for patients with severe hepatic impairment)

ARV = antiretroviral; AUC = area under the curve; AV = atrioventricular; BID = twice daily or every 12 hours; BSA = body surface area; BUN = blood urea nitrogen; CBC = complete blood cell count; CNS = central nervous-system; CYP = cytochrome P450; DXA = dual-energy x-ray absorptiometry; EC = enteric coated; ESRD = end-stage renal disease; IV = intravenous; LFT = liver function test; QD = once daily; RT = room temperature; SC = subcutaneously; TID = three times/day or every 8 hours; TIW = three times/week; UGT1 = UDP glucuronosyltransferase 1 family; wt = weight.
Information taken from Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. August 11, 2011. (Reference 28)

Most clinical data for pediatric and adult treatment-naive HIV-infected patients include three basic regimens: NNRTI-based (two NRTIs and NNRTI), PI-based (two NRTIs and PI), and NRTIs only (three NRTIs). Regimens that are NNRTI or PI based are preferred as initial therapy. Advantages and disadvantages of both NNRTI and PI ARV classes can be seen in Table 5 (Reference 29). Protease inhibitor–based regimens are preferred over NNRTI-based regimens in children younger than 3 years because of superior virologic suppression (References 69, 70). Nonnucleoside reverse transcriptase inhibitor–based regimens include either nevirapine or efavirenz. Efavirenz is commonly used in children 3 years and older. It was shown to be superior to nevirapine as first-line therapy in children and adolescents in Uganda (Reference 71). Unfortunately, there is no efavirenz pediatric formulation for children, limiting its use to those 3 years and older. Nevirapine is available as a palatable liquid formulation and may be an acceptable alternative to lopinavir/ritonavir in children younger than 3 years if they cannot tolerate lopinavir/ritonavir. However, nevirapine should not be used in infants who received nevirapine exposure as part of MTCT prevention (Reference 63). Etravirine is a second-generation NNRTI and can be used in treatment-experienced adolescents 16 years and older. This drug may be effective in patients who may have acquired resistance to efavirenz or nevirapine. Rilpivirine is the most recently approved NNRTI and is indicated for use in treatment-naive adults.

As previously noted, PI-based regimens are effective for treatment-naive pediatric patients with HIV. Protease inhibitors are coadministered with ritonavir because of its advantageous pharmacokinetic properties. Ritonavir is referred to as a "booster" because it is a strong CYP3A4 inhibitor that increases the concentrations of the other PIs by prolonging their half-life. Most clinical pediatric data exist for co-formulated lopinavir/ritonavir in infants and children older than 6 weeks. However, no efficacy data exist for comparison of this PI with other PIs in children. Another advantage of lopinavir/ritonavir is its different dosing formulations and its co-formulation with ritonavir. Other PIs include atazanavir, fosamprenavir, and darunavir coupled with low-dose ritonavir for use in children 6 years and older. If patients cannot tolerate ritonavir, the following PIs could be used in special circumstances: unboosted fosamprenavir in children 2 years and older, unboosted atazanavir in children 13 years and older weighing more than 39 kg, or nelfinavir in children 2 years and older. Extensive pediatric data exist for nelfinavir use, but it has varying rates of virologic potency. Studies have also reported correlation between nelfinavir trough concentrations and virologic response in treatment-naive pediatric patients (Reference 72). For example, for those who had trough concentrations less than 0.8 mg/L, only 29% of children had a virologic response. In contrast, virologic responses were observed in 80% of children who had trough concentrations greater than 0.8 mg/L. Furthermore, the pharmacokinetics of the nelfinavir pediatric powder formulation are extremely variable in children. However, nelfinavir tablets can be dissolved in water or

Table 5. Advantages and Disadvantages of NNRTI and PI ARV Classes (Reference 29)

Antiretroviral Class	NNRTIs	PIs
Advantages	• Lower pill burden • Convenience of use • Fewer metabolic complications (less dyslipidemia and fat maldistribution) than PIs • PI sparing • Long half-lives	• Virologic and immunologic efficacy well established • Higher genetic barrier to resistance (requires the accumulation of several mutations for class not to work) • Different mechanism of action from NNRTIs (do not act on same enzyme reverse transcriptase as NRTIs) • NNRTI sparing
Disadvantages	• Low genetic barrier to resistance (single mutation can confer resistance to class) • Rare but serious cases of rash and hepatotoxicity • Potential for several CYP450 drug interactions	• Higher pill burden • GI adverse effects • More metabolic complications (dyslipidemia, fat maldistribution, and insulin resistance) than NNRTIs • Potential for multiple CYP450 drug interactions • Poor palatability of liquid formulations, which may reduce adherence potential

ARV = antiretroviral; CYP = cytochrome P450; GI = gastrointestinal; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

other liquids to make an ingestible slurry, which showed pharmacokinetics similar to swallowing whole tablets in an adult study (Reference 73). Saquinavir is not recommended in children because of the lack of a pediatric formulation and limited dosing information, although it provides virologic and immunologic outcomes similar to lopinavir/ritonavir in adult treatment-naive patients (Reference 74). Indinavir is not recommended as initial therapy in children because there is no liquid formulation and it causes a high incidence of hematuria, sterile leukocyturia, and nephrolithiasis (References 75–78). Tipranavir is also not recommended as initial therapy because of limited data but may be considered in treatment-experienced children 2 years and older. Unlike in adults, once-daily dosing of darunavir, fosamprenavir, and lopinavir/ritonavir is not recommended in children because of the potential for increased clearance of these ARVs.

Triple NRTI regimens include zidovudine, lamivudine, and abacavir. These regimens are reserved for special circumstances in patients who are considered long-term nonprogressors and in those who cannot use PI- or NNRTI-based regimens because of significant drug-drug interactions, intolerance, or adherence concerns. An advantage of triple NTRI therapy is the availability of palatable liquid formulations and favorable tolerance. However, this combination has been shown inferior to efavirenz-based regimens in ARV-naive adults with a higher incidence and earlier time to virologic failure after 48 weeks of therapy (Reference 79). Other triple NRTI combinations are associated with poor virologic response because of the development of resistance to lamivudine (References 80, 81). Tenofovir, didanosine, and lamivudine combinations and tenofovir, abacavir, and lamivudine combinations are not recommended in children because of significantly increased rates of virologic failure in adults (References 82, 83).

Two NRTIs form the backbone of ARV treatment in combination with either a PI or an NNRTI. Six NRTIs are approved for use in children younger than 13 years: didanosine, zidovudine, lamivudine, stavudine, abacavir, and emtricitabine. Preferred dual NRTI combinations include abacavir or tenofovir or zidovudine with either lamivudine or emtricitabine. The most extensive clinical data in children are derived from the zidovudine and lamivudine combination, which is generally well tolerated. In a large retrospective study of children, zidovudine and didanosine showed the lowest toxicity rates (Reference 84). Emtricitabine and lamivudine are both cytosine NRTI analogs and can be substituted for one another. Some advantages of emtricitabine are its once-daily administration, possible coadministration with didanosine as a once-daily dual NRTI combination, and availability as a liquid formulation. However, didanosine requires fasting conditions for optimal absorption and is recommended only for children who can take it on an empty stomach. Abacavir and lamivudine is a potent dual NRTI combination for children, maintaining significantly better virologic suppression and growth rates (height and weight) than zidovudine and lamivudine or zidovudine and abacavir in 5 years of follow-up (Reference 85). However, a primary limitation of abacavir is the requirement for *HLA-B*5701* genetic testing before its use because of its association with hypersensitivity reactions. Prevalence of this genotype is more common in whites than in African Americans and Hispanics in the United States (8% vs. 2% to 2.5%). Genetic screening for *HLA-B*5701* before using abacavir has shown significant reductions in the hypersensitivity reaction from 7.8% to 3.4% (Reference 86). This testing should be done before considering abacavir for treatment of HIV-infected children, and abacavir should not be used in those who test positive for *HLA-B*5701*. Tenofovir may also be used with lamivudine or emtricitabine, but its preferred use is for HIV-infected adolescents who are 12 years and older in Tanner stage 4 or 5 or who are postpuberty because of the potential for adverse events such as decreased bone mineral density in young children. Other NRTI combinations include zidovudine and abacavir or zidovudine and didanosine. Dual NRTIs (e.g., stavudine with lamivudine or emtricitabine) are recommended only in special circumstances because stavudine is associated with mitochondrial toxicity, which could lead to a higher risk of lipoatrophy and hyperlactatemia than with other NRTIs (References 87–89). A stavudine and didanosine dual NRTI backbone is not recommended because of the higher rates of toxicity observed in adults such as neurotoxicity, pancreatitis, hyperlactatemia and lactic acidosis, and lipodystrophy compared with those taking zidovudine and lamivudine (References 90, 91). Other dual NRTI combinations that are not recommended are abacavir and didanosine, abacavir and tenofovir, and didanosine and tenofovir because of insufficient data in children. Of note, these dual NRTI combinations are not recommended as initial treatment for newly infected HIV-infected adults because of insufficient data and higher rates of resistance with some of the combinations. Furthermore, lamivudine and emtricitabine or stavudine and zidovudine combinations should not be coadministered because of competing pharmacologic activation pathways.

One of the problems in the treatment of HIV-infected children includes the scarcity of data regarding the newer ARVs such as rilpivirine, maraviroc, and raltegravir. These ARVs are not recommended as initial therapy for children because they have been studied and are approved only for treatment-naive adolescents 16 and older. Furthermore, one of the newer ARVs, etravirine, is only approved for treatment-experienced

adolescents 16 and older. In addition, the NRTI/NNRTI/PI combination and enfuvirtide are not approved for use as initial therapy in children. The risk of using the former combination is the development of multidrug class resistance, thus limiting future treatment options. Enfuvirtide is approved for use in treatment-experienced children 6 years and older in combination with other ARVs, with evidence of continuing viral replication despite current ARV therapy. Some of the main limitations to using enfuvirtide is that it is the only ARV given subcutaneously (twice daily), and local injection site reactions are very common (98%).

If first-line therapy with ARVs fails, defined as having a suboptimal virologic response to the current cART regimen, the etiology of treatment failure must be assessed before considering changes in ARV therapy. Treatment failure in many cases could be multifactorial; some of the most common reasons for treatment failure are inadequate adherence to ARVs, drug intolerance, pharmacokinetic variability and drug-drug interactions, or the presence of drug-resistant virus. First, adherence to ARVs should be evaluated. Adherence to therapy refers not only to taking medications according to their prescribed schedules, but also to the timing of the doses, food considerations with certain ARVs, and the avoidance of drug-drug interactions, especially given the wide availability of some herbal and over-the-counter products having important interactions with ARVs that could affect treatment response. Adherence plays a key role in the success of a treatment regimen because suboptimal adherence can lead to drug resistance and inadequate virologic control and has been associated with an increased risk of disease progression and mortality (Reference 92). If the patient has not been adherent to current ARVs, reasons for nonadherence should be addressed, and adherence to current ARVs should be reinforced, together with developing strategies to help patients overcome their adherence barriers. Drug intolerance may be one of the reasons for nonadherence to ARVs. If possible, adverse effects should be treated symptomatically, depending on severity. Pharmacokinetics, especially drug metabolism, may differ during puberty, necessitating a reevaluation of drug dosing, because some adolescents may require higher dosing by weight or by body surface area compared with adults. Concomitant drugs should be evaluated for each patient because drug-drug interactions could also be responsible for ARV treatment failure. If the patient has been adherent to ARVs and has not had a timely virologic response, then a genotype may be considered to determine whether the patient developed any resistance to current ARVs. However, if a patient is on a failing ARV regimen and no evidence of resistance is identified on a genotype, then poor adherence should be suspected.

Genotype resistance tests are recommended at baseline before starting ARV therapy. Genotypic assays can detect resistance to ARVs by PCR amplification and analysis of reverse transcriptase and protease coding sequences from a patient's HIV viral load. For these tests to be done, HIV viral load should be greater than 1000 copies/mL. Some of these tests might also be considered if a patient's viral load is between 500 and 1000 copies/mL. A specialist in pediatric HIV infection should be consulted for appropriate interpretation of genotypic results. Furthermore, the International AIDS Society-USA and the Stanford University HIV Drug Resistance Database are two useful resources that compile significant resistance-associated mutations to current ARVs (see www.iasusa.org/resistance_mutations or www.hivdb.stanford.edu). For the genotype to accurately reflect whether a patient may have resistance to the current ARV regimen, the patient must have been taking these ARVs within the past 4 weeks (i.e., drug-selective pressure). This is very important because reversion from resistant virus to wild-type virus can occur in the first 4 weeks after ARVs are discontinued. The genotype test should help elucidate which ARVs are still active for the patient. It is also critical to review ARV history as well as all other resistance tests when selecting a new ARV regimen because previous resistance tests may reveal archived resistance not evident on current resistance tests.

Other resistance tests such as phenotypic assays are reserved for those who have developed resistance to previous ARV regimens, especially PIs. These assays are useful in deriving a direct assessment of the effect and interaction of mutations acquired by viral strains on viral replication. Phenotypic assays involve PCR amplification of HIV gene sequences from a patient's viral strain, which are then inserted into a laboratory HIV strain. Replications of this recombinant viral strain at varying ARV concentrations are compared with the replication of a reference or wild-type viral strain. Fold resistance change is reported as the ratio of IC_{50} (median inhibitory concentration of ARVs needed to inhibit 50% of viral replication) of a patient's viral strain to IC_{50} of a reference strain. The greater the fold change, the more likelihood of ARV resistance. Two advantages of a genotype over a phenotype are a quicker turnaround time (1–2 weeks vs. 2–3 weeks) and a lower price. Virtual phenotypes are another type of resistance test that predicts the likelihood of a drug-resistant phenotype from a genotype. This test takes the patient's genotype and predicts a phenotype from a large known database of matching genotypes and phenotypes. This test may be insufficient for reliably detecting predictable phenotypes, especially with newer ARV drugs, because there may be fewer matching genotypes and phenotypes available for these drugs.

In addition to resistance testing history, factors to consider in creating a new ARV regimen should include ARV treatment history and toxicities, $CD4^+$ and viral load trends, adherence potential, and available treatment options. Furthermore, pill size, palatability, pill burden, and dosing frequency should be considered when developing a new ARV regimen. The goal of the new ARV regimen should be complete virologic suppression, ideally using three fully active drugs. If an HIV-infected child were on an NNRTI-based regimen and developed resistance to the NNRTI, a PI-based regimen would be recommended. If a child were on a PI-based regimen and developed resistance to the PI, an NNRTI-based regimen or an alternative PI-based regimen or a combination of an NRTI, an NNRTI, and an alternative PI regimen would be recommended. With respect to using potential NRTIs, special attention should be given to ensure the correct combination is used. For example, some patients can easily develop resistance to either emtricitabine or lamivudine if they are nonadherent to these NRTIs. If the patient has very few other NRTI mutations (especially thymidine analog mutations), using lamivudine or emtricitabine in a future treatment regimen can be advantageous because selection of a common mutation by these drugs could increase susceptibility to concomitant NRTIs such as tenofovir, stavudine, or zidovudine (References 93–95).

CCR5 tropism assays should be considered in adolescents 16 years and older to determine whether maraviroc is a feasible treatment option. Treatment-naive HIV-infected patients usually have CCR5 (R5) tropic virus. However, a co-receptor switch from CCR5 to CXCR4 (X4) or CCR5 to CCR5 and CXCR4 dual/mixed (D/M) tropic viruses is possible with time, especially in treatment-experienced patients and those who have HIV disease progression. The Trofile (Monogram Biosciences, South San Francisco, Calif.) phenotypic assay is used in the United States to determine CCR5 tropism. This assay usually takes about 2 weeks to report results and requires that the patient's viral load be greater than 1000 copies/mL. Of note, these assays have good sensitivity in detecting X4 or D/M tropic virus, representing up to 0.3% of the patient's plasma virus. Genotypic assays (Trofile DNA) recently became available in the United States, which are useful for detecting mutations associated with X4 or D/M tropic viruses. These assays also have the advantage of being able to be performed in patients with an undetectable viral load. Because maraviroc is a CCR5 antagonist, it is only effective for patients who have R5 tropic virus. Other ARVs such as etravirine and raltegravir are approved for treatment-experienced adolescents 16 years and older. Pediatric trials are under way to explore the feasibility of these newer ARVs. Should the patient have resistance to efavirenz or nevirapine, etravirine may still retain activity because at least three mutations are needed for this ARV to lose its potency.

Enfuvirtide and dual PI therapy may also be considered in children with extensive treatment resistance. Common dual PI combinations include lopinavir/ritonavir with saquinavir or atazanavir in both adults and children (References 96–101). However, some of the disadvantages of dual PI regimens are poor tolerability (particularly hyperlipidemia) and increased drug-drug interactions. Therapeutic drug monitoring (TDM) may be necessary to determine the appropriateness of target trough concentrations and will be discussed later. If a patient has very limited treatment options, children should be considered for newer therapeutic ARVs in clinical development. Information for clinical trials can be found at www.aidsinfo.nih.gov/clinicaltrials. If a patient has extensive treatment resistance, a pediatric HIV specialist should also be consulted, because he or she may have access to unpublished data regarding the efficacy and safety of newer agents approved for adults. Also worth noting, off-label use of newer ARVs in children should be done with caution because the adverse effects of these agents are unknown and may have observable differences in children compared with adults. Furthermore, changing pharmacokinetics in a growing child makes the extrapolation of dosing from adults to children on the basis of body weight or body surface area unpredictable and often may underestimate appropriate pediatric dosing, potentially leading to ARV resistance (Reference 102).

Antiretroviral treatment considerations may be different in certain special populations such as HIV-infected adolescents, HIV-infected women, those with HBV/HIV coinfection, and those with HCV/HIV coinfection. The largest percentage of HIV-infected children in the United States is made up of adolescents. Adolescents who acquire HIV infection sexually or by intravenous drug use follow a clinical course similar to that of adults compared with children, who are perinatally infected with HIV and have a long and complicated treatment history. Dosing of ARVs for adolescents can be complicated by factors such as Tanner staging of puberty and development of fat and muscles, which could influence drug pharmacokinetics. In children, dosing of ARVs may be higher than adult dosing to compensate for faster metabolism and/or higher drug clearance. Therefore, as a patient grows into adolescence, ARV dosing may be higher-than-usual adult dosing. Psychosocial and cognitive development may also present challenges for adolescents regarding adherence to ARVs. Some other challenges may be mood disorders and other mental illnesses that should be addressed adequately to ensure successful adherence to

ARVs. Directly observed therapy may be useful in these situations. The transition from adolescent care to adult HIV care settings can also be complicated and difficult. General guidelines regarding transitional plans and those who may benefit from them are available (References 103, 104).

Human immunodeficiency virus–infected women may have greater risks of certain adverse effects than men. These may include nevirapine-associated hepatotoxicity; lactic acidosis caused by prolonged exposure to NRTIs such as stavudine, zidovudine, and didanosine; and metabolic complications such as central fat accumulation and propensity to osteopenia/osteoporosis postmenopause (References 105–113). However, most of these differences do not require special treatment recommendations at this time. Sexually active females should be encouraged to use effective and consistent contraception methods. Efavirenz should not be used in adolescent girls who are sexually active and not using reliable contraception, or who want to become pregnant, because of the potential for neural tube defects that could occur in the fetus if used in the first trimester. In addition, PIs and NNRTIs may interact with oral contraceptives such as ethinyl estradiol, norethindrone, and norgestimate metabolites (norelgestromin and levonorgestrel) (Reference 29). Nonnucleoside reverse transcriptase inhibitors and boosted PIs are more likely to cause decreases in these oral contraceptives versus unboosted PIs such as atazanavir and fosamprenavir, which may actually increase concentrations. Alternative or an additional contraceptive method should be used in HIV-infected women who are using either NNRTIs or boosted PIs. Depot medroxyprogesterone acetate (DMPA) may also be an effective method of contraception, because some studies have shown unaltered efficacy of DMPA when coadministered with nelfinavir, efavirenz, or nevirapine regimens, as well as no additional adverse effects or significant changes in ARV drug concentrations (References 114, 115). Limited data exist for other forms of contraception such as vaginal rings and transdermal patches, but intrauterine devices have proven safe and effective in HIV-infected women (References 116, 117).

Choice of ARVs for HIV-infected pregnant women may be different from that for nonpregnant women (Reference 118). Initiation of ARV treatment is necessary, regardless of immunologic and virologic parameters, to prevent vertical transmission to the fetus. The goal of therapy is virologic suppression by the time of delivery, when transmission is more likely. Regardless of the antenatal regimen chosen in HIV-positive pregnant mothers, intravenous zidovudine should be administered to the mother during labor, and oral zidovudine should be given to the neonate for 6 weeks. Baseline resistance testing is also recommended before starting therapy. If the HIV-infected pregnant mother has no ARV resistance from genotypic assay, zidovudine plus lamivudine plus lopinavir/ritonavir should be the preferred ARV regimen. Standard ARV dosing of some PIs such as lopinavir/ritonavir may need to be increased during the third trimester to compensate for reduced bioavailability because of enhanced metabolism and increased clearance during pregnancy. Breastfeeding is also discouraged because of the high risk of transmission. Abrupt discontinuation of ARV therapy for the HIV-infected mother should be done cautiously because certain ARVs such as NNRTIs have a long half-life. Some experts recommend discontinuing NNRTIs at least one week before discontinuing other ARVs, and others recommend substituting an NNRTI with a PI plus two other ARVs for at least 30 days to reduce the development of NNRTI resistance (Reference 29).

If an HIV-infected child is acutely infected with hepatitis B virus (HBV) infection, the risk of developing chronic HBV is markedly greater in infants than in older children and adolescents (References 119–121). Very limited data exist for treatment of HIV/HBV-coinfected children. Only standard interferon alfa and lamivudine are FDA approved for treatment of children 2 years and older with chronic HBV. If treatment of chronic HBV is indicated in an HIV-infected adult, treatment of HBV should use fully suppressive cART with agents such as tenofovir and either emtricitabine or lamivudine, regardless of current $CD4^+$ cell count, and should also be considered in older children. Combination ARV therapy is important in this case to reduce the risk of developing resistance to ARVs. Caution must be used when discontinuing agents for treatment of chronic HBV because this could potentially cause hepatic damage secondary to reactivation of HBV. Furthermore, caution should be used when discontinuing ARVs that have activity against HBV; if this is the case, another active drug for HBV should be used to avoid a potential flare or reactivation of HBV. Alternative treatment strategies for chronic HBV may also include adefovir for older children who can receive adult dosing. Limited data on peginterferon alfa, entecavir, and telbivudine preclude their use in coinfected children at this time.

The prevalence of hepatitis C virus (HCV) in HIV-infected children is as much as 3.1% in the United States (References 25, 122). Insufficient data exist for both HCV disease progression and treatment of HCV in coinfected children. Coinfected adults with chronic HCV have a higher risk of progressing to cirrhosis than do those with HCV infection alone, especially when $CD4^+$ cell counts are less than 350 cells/mm^3. If treatment of HCV is indicated, preference is given to those whose $CD4^+$ cell counts are greater than 200 cells/mm^3 because better immunologic status will likely improve

HCV treatment response (References 123–126). If $CD4^+$ cell counts are below 200 cells/mm^3, ARV therapy should be initiated and HCV treatment delayed until $CD4^+$ cell counts rebound. Because no studies of coinfected children have been conducted, recommendations are extrapolated from data in adults. Treatment of HCV in coinfected adults includes pegylated interferon alfa-2a or -2b plus oral ribavirin for 48 weeks regardless of HCV genotype. Combination therapy with interferon alfa and ribavirin for 48 weeks is also recommended in HIV/HCV-coinfected children who are 3 years and older. Other treatment options for HCV may include the recently approved PIs boceprevir and telaprevir. However, these drugs are not yet approved for treatment of HCV in HIV-infected patients because use of these drugs will be complicated by several drug interactions. In addition, the role of these drugs for children is unclear because monoinfected HCV studies were conducted only in adults. Didanosine, zidovudine, and stavudine should be avoided when using ribavirin because these NRTIs may lead to mitochondrial and hematologic toxicities. Treating both HCV and HIV can result in drug-induced liver injury with substantially elevated liver enzymes; associated ARV agents include stavudine, didanosine, nevirapine, full-dose ritonavir, or tipranavir boosted with low-dose ritonavir (Reference 127). Dose modification or avoidance of some hepatically metabolized ARV agents may be necessary, depending on the severity of liver disease (particularly Child-Pugh class B and C disease). Antiretroviral therapy may be beneficial in patients coinfected with HCV because it may slow the progression to liver disease and reduce HIV-related inflammation associated with lower $CD4^+$ cell counts.

Monitoring of Therapy

Therapeutic Outcomes

Before initiating ARV therapy, several parameters related to laboratory testing and factors that may affect treatment adherence should be assessed at baseline. Laboratory testing should include $CD4^+$ count and $CD4^+$ percentage, HIV viral load, serum chemistries, lipid panel, hematologic panel, resistance testing (in some cases, it may be prudent to initiate therapy before resistance testing, with the understanding that therapy may require modification upon the availability of those results), and any other laboratory parameter that may be affected by the choice of ARV regimen. After ARV therapy is initiated or changed, HIV-infected children and adolescents are monitored for the regimen's efficacy, safety (toxicity, adverse effects), tolerability (medication palatability, dosing frequency, pill burden), and adherence to the regimen. For patients on ARV therapy, the following laboratory parameters are recommended for monitoring at baseline; at 4–8 weeks; and then every 3–4 months once stable: $CD4^+$ count, $CD4^+$ percentage, HIV viral load, complete blood cell count with differential, and serum chemistries. A lipid panel may be drawn every 6–12 months. More frequent monitoring of HIV surrogate markers may be required for patients who are experiencing virologic, immunologic, or clinical failure.

When monitoring the efficacy of ARV treatment, some patients may not have positive $CD4^+$ and viral load trends. If this occurs, treatment failure may be considered and can be classified as virologic, immunologic, or clinical. Virologic failure may be defined as either not achieving viral suppression or the occurrence of viral rebound after viral suppression. An incomplete virologic response in children is defined as less than a 1-log decrease in viral load from baseline after 8–12 weeks of ARV therapy, a viral load above 400 copies/mL after 6 months of treatment, or a detectable viral load after 12 months of treatment (optimal viral suppression is less than 20–75 copies/mL, depending on the sensitivity of the assay used). Viral rebound is defined by repeated detectable viral loads after a period of viral suppression. Repeated viral loads greater than 1000 copies/mL are indicative of virologic failure in children (Reference 28).

Assessing immunologic response in children is difficult because of the variability in $CD4^+$ count that occurs in children younger than 5 years. For this reason, $CD4^+$ percentage (which has less variability) is considered a more reliable measure of immune status in children younger than 5 years. For older children, the absolute $CD4^+$ count may be used for monitoring immunologic status.

Immunologic failure may be classified as an incomplete response to ARV treatment or as continued immunologic decline. An incomplete response to treatment is characterized differently on the basis of age. For patients younger than 5 years, it is described as not achieving an increase of 5 percentage points or more in $CD4^+$ levels in those presenting with a $CD4^+$ percentage less than 15. For patients 5 years and older, it is described as failing to increase $CD4^+$ levels by 50 cells/mm^3 or more over baseline within the first year of therapy in those presenting with $CD4^+$ counts less than 200 cells/mm^3. Patients with low pretreatment $CD4^+$ counts are at greater risk of experiencing a blunted immunologic response despite virologic suppression. In addition, some ARVs or ARV combinations may contribute to a suboptimal immunologic response (ex. myelosuppression related to zidovudine therapy; the combination of tenofovir and didanosine has been associated with a decline in $CD4^+$ count; therefore, their concomitant administration is not recommended). Immunologic decline is characterized as a steady decrease

of 5 percentage points in $CD4^+$ percentage below baseline, regardless of age, or as a decrease in $CD4^+$ count to below baseline levels in children 5 years and older (Reference 28).

Clinical failure may be identified through the presence of opportunistic infections or disease progression. However, it is important to consider a patient's immunologic and virologic status in the presence of clinical symptoms because those symptoms may not necessarily represent treatment failure. Factors in disease progression that can represent treatment failure in children include failure to grow at a normal rate even when nutritional requirements are met, recurrent infections that may be indicative of progression to AIDS, and impairment in cognitive and motor skills development (Reference 28).

When assessing treatment failure in HIV-infected children, several factors should be considered before modifying ARV therapy. Some of these include pharmacokinetic variability, drug toxicity, and ARV resistance. However, one of the most significant factors affecting treatment outcome is adherence to ARVs. Low rates of adherence to ARVs have been linked to virologic failure, with that risk increasing as more ARV doses are missed. Low adherence rates can also increase the risk of developing ARV resistance, with the potential for cross-resistance if mutations continue to accumulate while a patient is on a suboptimal regimen. This, in turn, could limit future treatment options. On the contrary, high adherence rates are associated with viral suppression, low rates of drug resistance, increased survival rates, and improved quality of life. Although a 95% adherence rate has historically been desired to achieve and maintain virologic suppression, it is possible to do so with lower rates, depending on the medications used for treatment, including some boosted PI-based regimens and those containing efavirenz plus two NRTIs (References 27, 128). It is difficult to predict high or low adherence rates in children because not only do they have their own adherence barriers to overcome, but they may also have to deal with any adherence barriers their own caregivers introduce. Factors that influence adherence rates may include the following: frequency of dosing, pill burden, ARV palatability, refusal of ARVs, forgetfulness, no established daily routine, ARV-related adverse effects, and psychosocial issues (financial concerns, housing stability, transportation limitations, social/familial support, stigma, psychiatric disorders, and active substance abuse) (References 28, 92). In hospitalization cases, it is important that the medical team be in contact with the patient's ambulatory HIV care provider to maintain appropriate HIV treatment (correct medications and doses), ensure continuity of care, recognize the potential for drug-drug interactions with ARVs (e.g., PIs and NNRTIs are metabolized extensively through the CYP system), and discharge patients on appropriate therapy for HIV and any comorbid condition to maximize therapeutic benefit and minimize adverse events.

Children must depend on their caregivers to administer their drugs appropriately; therefore, any adherence barriers that affect the caregiver may also directly affect the success or failure of the child's treatment regimen. Caregivers may struggle with the decision to disclose a child's status to family or friends, which may lead to disguising or hiding prescription labels, not refilling medications in a timely manner, and skipping doses when away from the home. Furthermore, in vertical transmission, parents may have feelings of guilt or regret and seek to avoid reminders of their own HIV status (Reference 28).

Adherence to ARVs in HIV-infected adolescents may be influenced by various factors. These patients are very concerned with being perceived as different from their peers, and they may refuse to take their ARVs. They may skip doses to avoid disclosing their status to their peers. In vertical transmission, many adolescents have been taking ARVs for several years, and it is not unusual for them to experience pill fatigue. Instability in the home, mental health issues, neurocognitive delay, and active substance abuse may also negatively affect a patient's ability to remain adherent to a drug regimen. Educating patients, as well as caregivers, on the need to maintain a consistently high rate of adherence to the ARV regimen for achieving therapeutic goals and to avoid the development of drug resistance and providing them with strategic tools to help overcome adherence barriers are essential to achieving therapeutic goals, avoiding medication errors, and empowering patients to take control of their health care.

Because many of the adherence barriers previously described are perceived by patients and caregivers as of more immediate concern than taking their ARVs consistently, it is essential to work with them to overcome these barriers. Although studies of the adolescent population have used technology, peer support groups, and motivational interviewing techniques to improve adherence and virologic outcomes, their positive effects have been short-lived (References 129, 130). Several strategies may still be employed by the health care team to help patients/caregivers attain a higher rate of adherence to ARVs. Some of these may include using a multidisciplinary approach to care, providing referrals for specialty services (medical and/or social), maintaining effective communication/follow-up, assessing adherence rates/barriers at each medical visit, and providing adherence tools (pillboxes, visual aids) to the patients. Antiretroviral regimens should be tailored to a patient's lifestyle with respect to dosing frequency, tolerability profile (e.g., potential adverse effects, drug interactions),

and the patient's daily routine. Educating both patients and caregivers on the importance of ARV adherence, working with them to establish a plan to manage potential adverse effects of ARVs, identifying adherence barriers and the reasons behind them, and encouraging a reliable support system are critical for optimizing adherence to ARVs (Reference 92).

Therapeutic Drug Monitoring

Therapeutic drug monitoring looks at drug concentration measurements to determine appropriate drug dosing to minimize adverse effects while achieving/maintaining positive treatment outcomes. Therapeutic drug monitoring is typically employed as a therapeutic management strategy, with medications used to treat seizures, heart arrhythmias, and bacterial infections. Because of inter-patient variability in plasma concentrations of certain NNRTIs and PIs, low plasma concentrations of ARVs that can lead to decreased treatment response, and high concentrations that can lead to toxicities for certain ARVs, TDM may occasionally be employed in the therapeutic management of pediatric patients with HIV. However, there are insufficient data that correlate TDM with positive changes in virologic or clinical outcomes. Furthermore, definitive therapeutic ranges for maximizing clinical response and minimizing adverse effects are not well established for all ARVs, and few laboratory facilities within the United States are adequately equipped to perform TDM with ARVs. Although not recommended for routine use in HIV management, TDM may be useful in the following instances: as a tool to help explain a suboptimal treatment response; for a drug-resistant virus—comparing drug concentration with virus susceptibility; for medication administration issues—crushing/chewing/dissolving a medication may change the pharmacokinetics of a drug, dietary habits may alter a medication's pharmacokinetic profile, and incorrect dosing may occur because of administration errors by caregivers; for problems related to adherence that lead to low plasma concentrations of ARVs such as missed doses or inconsistent dose timing; as a tool for identifying drug toxicity that may be caused by an agent exceeding the normal therapeutic range; and for identifying drug interactions—many ARVs have significant interactions with other medications and/or food that could lead to altered plasma concentrations (References 28, 29).

Adverse Effects

Table 4 summarizes common adverse effects of ARVs and their management as well as relevant monitoring parameters. Class-related adverse effects of NRTIs include lactic acidosis and hepatic steatosis. These are commonly representative of prolonged stavudine, didanosine, or zidovudine use. Lactic acidosis is characterized by fatigue, weakness, myalgia, weight loss, and unexplained nausea or vomiting. Although it is rare, some patients present with acute organ failure such as fulminant hepatic, pancreatic, and respiratory failure. Blood lactate concentrations are considered in those with clinical signs and symptoms consistent with lactic acidosis. If lactic acidosis and hepatic steatosis occur with stavudine, zidovudine, or didanosine, switching to tenofovir or abacavir with either emtricitabine or lamivudine may be appropriate because these agents tend to have less mitochondrial toxicity. Some physicians will use an NRTI-sparing regimen, when possible, if the lactic acidosis is severe. Facial or peripheral lipoatrophy is also commonly associated with thymidine analog NRTIs such as stavudine and zidovudine, as well as didanosine. Lipoatrophy is manifested as a loss of subcutaneous fat in the face, buttocks, and extremities. If lipoatrophy is present, switching from zidovudine or stavudine to another NRTI that has less mitochondrial toxicity and is active against HIV may help reduce further progression of lipoatrophy. Diminished bone density (osteopenia and/or osteoporosis) is also a possible adverse effect with tenofovir, stavudine, or PIs. Monitoring should include serum 25-hydroxyvitamin D concentrations and DXA (dual-energy x-ray absorptiometry) scans. Appropriate management may include sufficient calcium and vitamin D supplementation and avoidance of steroids and medroxyprogesterone, if possible. The role of bisphosphonates in children is not established, but considering ARVs other than tenofovir, stavudine, or PIs may reduce the incidence of osteopenia and osteoporosis.

Class-specific adverse effects of PIs include dyslipidemia, hyperglycemia, prolonged PR interval (first-degree symptomatic atrioventricular block), fat maldistribution, increased bleeding episodes in patients with hemophilia, elevated liver enzymes, and gastrointestinal intolerance such as diarrhea. Lipodystrophy and central lipohypertrophy are mostly associated with PIs. These may manifest as central fat accumulation in the abdomen, trunk (gynecomastia), or back of neck (buffalo hump). Lipodystrophy is more common in adolescents than in children. Lifestyle modification including exercise and diet or using other ARVs may help with the management of central lipohypertrophy. Of note, liposuction, metformin, and rosiglitazone are not useful for treatment in children. Tesamorelin was recently approved for treatment of lipodystrophy in HIV-infected adults, but efficacy and safety have not been established in children. Effects of PIs on dyslipidemia are related to ritonavir dosing; higher ritonavir doses lead to worsening effects of dyslipidemia, especially hypertriglyceridemia. For PI use, the following should be monitored routinely: lipid panel (total

cholesterol, triglycerides, LDL-C [low-density lipoprotein cholesterol], and HDL-C [high-density lipoprotein cholesterol]), blood glucose, and liver enzymes. If triglycerides are greater than 500 mg/dL, the risk of pancreatitis is increased. Although fibrates are only approved for adults, one study showed that fibrates significantly decreased triglyceride levels among children in clinical practice (Reference 131). Primary pharmacologic interventions used for the treatment of dyslipidemia in HIV-infected children include fish oils and some statins. Fish oils containing PUFAs (n-3 polyunsaturated fatty acids) may be considered, as well as pravastatin 20 mg once daily for children 8–13 years of age and 40 mg once daily for adolescents 14–18 years of age, atorvastatin 10–20 mg once daily for children older than 6 years, and rosuvastatin 5–20 mg once daily for those 10–17 years of age (Reference 28). Dyslipidemia should be appropriately treated with drugs, when necessary, or switching to alternative ARVs, which have less effect on dyslipidemia. Caution should also be used when taking ARVs with certain statins because drug-drug interactions are possible. Lovastatin and simvastatin are contraindicated with PI use. Protease inhibitors should also be used with caution in those with preexisting cardiac conduction problems or those taking other drugs such as calcium channel blockers, β-blockers, digoxin, and verapamil because these are known to prolong the PR interval. Rash is also possible with some of the PIs, especially with fosamprenavir, tipranavir, and darunavir, which possess a sulfonamide moiety. Mild to moderate rash can be treated with antihistamines with continuation of ARVs. For patients who develop a severe rash such as Stevens-Johnson syndrome, all ARVs should be discontinued. The FDA recently issued a new warning for labeling for lopinavir/ritonavir regarding a serious health problem reported in premature babies receiving lopinavir/ritonavir oral solution (Reference 132). The oral solution contains alcohol and propylene glycol; premature babies have a decreased ability to eliminate propylene glycol, which has led to adverse events such as serious heart, kidney, or breathing problems.

Class-related adverse effects of NNRTIs include rash and elevated liver enzymes. Limitations for efavirenz use include central nervous system adverse effects such as fatigue, insomnia, vivid dreams, depression, suicidal ideation, poor concentration, and agitation. If any of these adverse effects occur, they are usually transient and should subside after 2–4 weeks. Some patients, particularly African Americans, may have a genetic polymorphism in the CYP2B6 enzyme, which could exacerbate the adverse effects of efavirenz (Reference 133). If a patient has underlying depression or other preexisting psychiatric conditions, caution should be used when considering efavirenz because it could exacerbate or worsen depression. Of note, efavirenz is the only ARV with a pregnancy category D rating, which assumes potential teratogenicity to the fetus should efavirenz be used during the first trimester of pregnancy. Efavirenz is not recommended in adolescent females who are sexually active and may become pregnant unless reliable contraception is used. Major limitations for nevirapine use in children are higher rates of toxicity, which may include rare cases of hypersensitivity reactions including Stevens-Johnson syndrome and life-threatening hepatitis. Hepatic toxicity tends to be less common in children than in adults who receive chronic nevirapine (References 134, 135). Rash and elevated liver enzymes occur more commonly in females than in males, and nevirapine should not be initiated in women whose $CD4^+$ cell counts are greater than 250 cells/mm^3 or in men whose $CD4^+$ cell counts are greater than 400 cells/mm^3 because of the increased risk of liver toxicity observed when nevirapine is initiated above these $CD4^+$ cell thresholds (Reference 136).

The severity of adverse effects experienced with ARVs determines whether these medications are discontinued. Some mild or moderate adverse effects of ARVs such as diarrhea or mild rash can be treated symptomatically without discontinuation or substitution of ARVs. However, some adverse effects may be more severe and necessitate a change in ARV therapy. If the responsible ARV agent can be identified, caution should be taken to make sure that an active ARV is substituted. Careful attention should be given to history of treatment with ARVs and resistance testing when selecting an alternative ARV. If adverse effects are severe or life threatening, all ARVs should be discontinued at the same time. Once the patient is stabilized, implementation of a completely new ARV regimen that does not include the prior offending agent should be considered.

Conclusions

The availability of newer ARV agents and new research on the progression of disease and the efficacy and safety of treatment modalities will continue to affect the management of HIV infection in the pediatric and adolescent populations. It is important to consider a patient's individual characteristics (e.g., past ARV exposure, resistance profile, comorbid conditions, additional drug therapy, family/social situation) when determining an appropriate initial or modified treatment regimen to maximize effect and minimize adverse events. The treatment of HIV infection in children and adolescents is not simplistic, and a specialist in this field should be consulted when necessary.

Clinical Caveats for Pediatric HIV Infection

- Since the development of the first PI in the mid-1990s, potent combination ARV therapy has transformed HIV infection from a death sentence to a chronic disease state.
- HIV-infected children are living longer and are able to experience a better quality of life because of an armamentarium of newer ARVs that are more potent, convenient, and tolerable.
- One of the best ways to prevent HIV transmission is to use safe sex practices such as condoms (especially important for adolescent population).
- Early initiation of ARV therapy leads to improved virologic, immunologic, and clinical outcomes.
- Many factors must be considered when initiating ARV therapy in children from both the medical and psychosocial standpoint, including appropriateness of certain medications for particular age groups, regimen complexity and palatability, adherence barriers, and issues affecting caregivers.
- Adherence to ARVs should be assessed and evaluated at every chance because this is critical to ensure positive treatment outcomes.
- Treatment failure can be multifactorial; most common reasons are nonadherence to ARVs, drug intolerance, pharmacokinetic variability, drug-drug interactions, or the presence of drug-resistant virus.
- An interdisciplinary health care team approach including physicians, pharmacists, nurses, social workers, dietitians, and others is essential in optimizing care for HIV-infected children.

Additional Resources

Additional information may be found on the following Web sites:

1. AIDSinfo, provided by the U.S. Department of Health and Human Services, www.aidsinfo.nih.gov
2. Centers for Disease Control and Prevention, www.cdc.gov
3. The National Institutes of Health, www.nih.gov
4. The HIV Medicine Association of the Infectious Diseases Society of America, www.hivma.org
5. The Pediatric Infectious Diseases Society, www.pids.org

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CHAPTER 43

Parasitic Infections in Pediatrics

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Learning Objectives

1. List the most common types of parasitic infections seen in the United States.
2. Identify complications in children who are infected with parasites.
3. Describe the routes of infection of parasites in children.
4. List preventive steps for avoiding parasitic infections.
5. Identify two options for prophylaxis of malaria in children.
6. Discuss treatment options for malaria infection in children.
7. Identify routes of infection of toxoplasmosis in children.
8. List effective therapies for ascariasis and enterobiasis.
9. Explain the transmission, etiology, and epidemiology of lice and scabies.
10. Explain the differences in pharmacologic versus nonpharmacologic treatment plans for lice.

Abbreviations in This Chapter

CDC	Centers for Disease Control and Prevention
FDA	U.S. Food and Drug Administration
HIV	Human immunodeficiency virus
O&P	Ova and parasites
PCR	Polymerase chain reaction

For coverage of cryptosporidiosis, see the Infectious Diarrhea chapter.

Introduction

Parasitic infections, which are common worldwide, are associated with significant morbidity and mortality. The greatest impact of these infections is seen in developing countries in Central and South America, Africa, and Asia (Reference 1). In the United States, those likely to become infected are immigrants and travelers from endemic countries, as well as individuals with immunocompromised conditions such as AIDS (acquired immunodeficiency syndrome).

Parasites are seen more often in areas where sanitation is suboptimal, and they are spread through contact with food or water contaminated with fecal matter. However, other routes of transmission include contact with infected dirt, contaminated freshwater, or an insect vector, such as a mosquito bite. Although rare, transmission may also occur through blood transfusion, by sharing of infected needles, or congenitally from mother to baby.

A parasite lives in or on another species (the host) to survive, using the host for food, water, or shelter. Parasites may infect their host by being ingested or through the external surface. Some parasites will require several hosts of different species to complete their life cycles. Parasites typically cause some degree of injury to the host. The extent of injury depends on factors such as parasite load as well as on the nutritional status and immunologic competence of the host. Parasitic infections in children may lead to malnutrition and stunted growth and development, especially chronic infections in the gastrointestinal tract (References 2, 3).

Parasites are defined as eukaryotic unicellular or multicellular microorganisms. They are usually classified into two groups: single-celled protozoa and multicellular helminthes, including worms. Protozoa that multiply in their human hosts may increase in number to cause overwhelming infection. By contrast, helminthes have life cycles that are more complex and that typically involve substantial time outside their human hosts. As they migrate through tissue, they may cause systemic reactions. This chapter will focus on parasitic infections most commonly seen in children in the United States and will be divided into three main sections: (1) protozoa, both gastrointestinal and systemic; (2) helminthes; and (3) ectoparasites, including lice and scabies.

Gastrointestinal Protozoa

Giardia

Giardiasis is caused by *Giardia intestinalis*, also known as *Giardia lamblia* and *Giardia duodenalis*. Humans, as well as domesticated animals and wildlife, can be infected with *Giardia*. The most common animal reservoirs include beaver, cattle, dogs, rodents, and bighorn sheep (Reference 4). This flagellated protozoan is the most common intestinal parasitic cause of enteritis worldwide and the second most common in the United States: in 2009, there were 19,399 cases reported to the Centers for Disease Control and Prevention (CDC)

(References 5, 6). Children aged 1–9 years are considered a high-risk group, and they may transmit the infection to their caregivers (Reference 6). Each year, there is a seasonal variation, with spikes of cases seen in the United States between June and October.

Giardia is transmitted by the fecal-oral route; thus, the incidence is higher in populations with poor sanitation. It may also be contracted through close contact with infected individuals (Reference 5). *Giardia* cysts are ingested through fecally contaminated sources, often water, but they may be ingested through fecal-oral transmission. *Giardia* is resistant to the chlorine levels in normal tap water. Because *Giardia* survives well in cold mountain springs for extended periods, giardiasis often occurs in those who camp, backpack, or hunt; it has been called "backpacker's diarrhea" or "beaver fever" (Reference 5). The relative infectious dose is small; as few as 10–25 cysts may cause infection in humans (Reference 5). Once the cysts are ingested, they are activated in the acidic environment of the stomach, where they produce two trophozoites. These trophozoites migrate to the duodenum and proximal jejunum, attach to the mucosal wall, and replicate. This results in malabsorption, dyspepsia, and diarrhea. Trophozoites can transform into cysts and pass back into the feces, where they are excreted. They can remain actively infectious for months in a moist environment (References 5, 6).

Clinical presentation can vary between individuals, but it typically includes symptoms of diarrhea, abdominal cramps, bloating, weight loss, and malabsorption that may have had a gradual onset and lasts for 2–4 weeks (References 5–7). An incubation period of 1–2 weeks will typically precede symptoms. Chronic giardiasis may develop after the acute infection if not treated appropriately. Symptoms of chronic infection vary but may include loose stools, steatorrhea, malabsorption, weight loss of 10% to 20%, fatigue, and malaise that may last for months (Reference 5). Some patients exhibit rash as part of a sensitivity reaction.

Because *Giardia* infection is noninvasive, the gold standard for diagnosing giardiasis is stool studies for ova and parasites (O&P). Cyst excretion can be found in both formed and loose stools, whereas trophozoites are mostly found in diarrhea. Examination of a single stool specimen has a sensitivity of 50% to 70%, but the sensitivity increases to 85% to 90% with the use of three serial stool samples (Reference 7). Fecal immunoassays, such as direct fluorescent antibody testing, are very sensitive and specific and may be used to confirm diagnosis (References 8–11).

The treatment goal in *Giardia* infections is to eradicate the organism, which will resolve the diarrhea, malabsorption, and other symptoms. The drug of choice is oral metronidazole, administered three times/day for 5–7 days (Table 1). Typical cure rates with metronidazole range from 80% to 95% (References 7, 14). In pediatric patients too young or unable to swallow a tablet, a liquid preparation may be required; however, there is no commercially available preparation. Metronidazole suspension can be extemporaneously compounded; however, the taste of these preparations is often foul, and some children will not tolerate it. An alternative

Table 1. Medications for *Giardia* Infections (References 15, 51)

Medication	Pediatric Dosage (Oral)	Dosage Forms	Common Adverse Drug Reactions	Comments
Albendazole	10 mg/kg/day once daily for 5 days (max dose 400 mg/day)	Tablet: 200 mg	Abdominal pain, nausea, headache	Tablets may be crushed or chewed.
Metronidazole	15–30 mg/kg/day in divided doses every 8 hours for 5–7 days (max dose 750 mg/day)	Capsule: 375 mg Tablet: 250 mg, 500 mg	Nausea, headache	May compound oral suspension 50 mg/mL (Reference 12)
Nitazoxanide	Children 1–3 years: 100 mg every 12 hours for 3 days Children 4–11 years: 200 mg every 12 hours for 3 days Adolescents ≥ 12 years: 500 mg every 12 hours for 3 days	Suspension: 100 mg/5 mL Tablet: 500 mg	Abdominal pain, diarrhea, nausea, headache	Store reconstituted suspension at room temperature. Discard unused portion after 7 days.
Tinidazole	50 mg/kg once (max dose 2 g)	Tablet: 250 mg, 500 mg	Nausea, altered sense of taste	Only in children > 3 years Oral suspension 67 mg/mL can be compounded (Reference 13) Take with food.

product, nitazoxanide, is U.S. Food and Drug Administration (FDA) labeled for the treatment of *Giardia* infections in both pediatric and adult patients and is commercially available in both tablet and suspension formulations. Nitazoxanide should be administered every 12 hours for 3 days, and it may be taken with food to minimize gastrointestinal upset. Other alternative products include albendazole, an antihelminthic, and tinidazole. Albendazole has been shown to be as effective as metronidazole in treating *Giardia* infections in pediatric patients (Reference 15). This is a good option in children with mixed helminth and *Giardia* infections. A single dose of tinidazole may be more effective than metronidazole or albendazole in children older than 3 years; however, like metronidazole, tinidazole is not commercially available as an oral liquid preparation and will need to be extemporaneously compounded.

Patients being treated for giardiasis should be monitored for resolution of symptoms, including reduction in diarrhea, resolution of bloating and abdominal cramps, and improved oral tolerance. It is especially important to monitor for signs and symptoms of dehydration and weight loss in children and to initiate oral rehydration as necessary. Diarrhea may begin to resolve in a few days but can take as long as 1–2 weeks for full resolution. Some patients may develop post-*Giardia* lactose intolerance and will improve with the institution of a lactose-free diet. Patients who appear unresponsive to treatment should be evaluated for possible reinfection or antibiotic resistance. Patients with reinfection who initially received a course of metronidazole should receive a second course of 5–7 days, or they may be treated with one of the alternative medications. Patients with true antibiotic resistance should be treated with an alternative medication (Reference 15).

Strategies for preventing giardiasis include proper and frequent handwashing and use of proper sewage disposal and water treatment. In endemic areas, ingestion of bottled water is preferred to consumption of tap water or from freestanding bodies of water. In day care settings, proper disposal of diapers, as well as exceptional handwashing techniques when changing soiled diapers, should be employed. When intake of potentially contaminated water is necessary, giardiasis may be prevented by boiling water for 1 minute (at altitudes higher than 6562 ft, boil for 3 minutes), heating water to 158˚F (70˚C) for 10 minutes, using portable camping filters, or using iodine purification tablets in potable water (Reference 16).

Amebiasis

Entamoeba are nonflagellated protozoa that are ubiquitous worldwide, but they do not typically cause pathogenic diseases in human hosts. The exception is *Entamoeba histolytica*, which causes amebic colitis and liver abscess. *E. histolytica* is most prevalent in tropical and developing countries (Reference 10). Worldwide, about 10% of the population is infected, 90% of whom are asymptomatic (Reference 4). Of the 10% who are symptomatic, there are around 100,000 deaths annually, making *E. histolytica* the world's second leading cause of protozoan-related death after malaria (Reference 6). Most cases in the United States occur in travelers returning from endemic countries or in recent immigrants from Mexico, India, West and South Africa, and parts of Central and South America. In the United States, the prevalence of amebiasis is about 4% of the general population (Reference 17). Infection is common in individuals with compromised immune systems (Reference 6). Transmission is by the fecal-oral route and is increased by crowding and poor sanitation.

The infective cysts of *E. histolytica* are ingested and hatch into trophozoites in the small intestine, where they continue through the digestive tract to the colon. Some of these trophozoites become cysts that are passed into the feces; after they are excreted, they can survive for months in a moist environment, like *Giardia*. However, trophozoites can also invade the intestinal mucosa and produce flask-shaped ulcers in the submucosa; they may spread to the liver, lungs, and brain through the bloodstream (References 6, 7, 17). The intestinal ulcerations may bleed and lead to colitis within 2–6 weeks of the initial infection (Reference 16). Colitis is followed by weight loss, severe abdominal pain, bloody diarrhea, malaise, and fever. A chronic active infection of *E. histolytica* may mimic the symptoms of inflammatory bowel disease. In disseminated disease, trophozoites penetrate the mucosal wall, enter the liver, and release toxins that cause hepatocyte damage and lead to amebic liver abscesses and periportal fibrosis, usually within 5 months of the initial infection (Reference 6). Amebae are chemotactic, which may lead to a significant leukocytosis with left shift and high temperature. Other objective findings include elevated alkaline phosphatase, liver tenderness, dull pleuritic right upper quadrant pain that radiates to the right shoulder, and hepatomegaly (References 6, 17, 19). Liver abscesses can spread to the lungs and pleura and may rupture into the pericardial, peritoneal, or pleural spaces (Reference 6).

Effective diagnosis relies on a reliable patient history, including any recent international travel, as well as serial stool samples for O&P and an *E. histolytica* stool antigen test (References 6, 17). Because only 10% to 35% of patients with liver abscesses have concomitant gastrointestinal symptoms, magnetic resonance imaging, serology, and liver ultrasonography should be performed if amebic liver involvement is suspected (Reference 17). Biopsy may be needed.

The goal of therapy for amebiasis is to eradicate the parasite by amebicides. However, supportive care may be necessary for 6 months to 1 year as the ulcerations and abscesses resolve and heal (Reference 6). Because of the different manifestations of amebiasis, including invasive liver abscess, intraluminal colitis, or asymptomatic cyst carriage, drug therapy may differ, depending on the type and site of infection. Asymptomatic cyst carriers should receive either oral paromomycin every 8 hours for 7 days or oral iodoquinol every 8 hours for 20 days (Table 2). These treatments have cure rates of 84% to 96% (Reference 20). These agents act only in the lumen of the intestines and are only minimally absorbed by the gastrointestinal tract. The mainstay for invasive amebiasis is oral metronidazole taken three times/day for 7–10 days. Once-daily tinidazole for 3–5 days may be used in children older than 3 years for both localized intestinal and invasive infections. Both erythromycin and tetracycline may be used in patients with contraindications to or intolerance of metronidazole or tinidazole. After completing the treatment course for invasive amebiasis, patients should receive a full course of a luminal amebicide (paromomycin or iodoquinol) to ensure complete eradication (Table 2).

Drug effectiveness should be monitored by resolution of symptoms, and by repeat negative stool examinations after 5–7 days of treatment, at the end of the treatment course, and at 1 month after therapy is completed. Intestinal symptoms will abate within 3–5 days of treatment initiation. Patients with colitis may need a colonoscopy if serial stool samples are negative. Colonoscopy with tissue sample may be able to identify amebiasis in patients with bloody diarrhea if other tests are inconclusive. In invasive disease, serology should be monitored for resolution at end of treatment and 1 month after completion of therapy. Patients with liver abscesses may require repeat imaging, although some radiographic evidence of liver abscesses may persist for up to 1 year after the end of treatment (Reference 20).

Prevention of amebiasis includes the use of proper sanitation to eradicate the carriage of cysts. Travelers to endemic areas should be cautioned to avoid the consumption of unpeeled fruit and vegetables, salads, ice cubes, and untreated water. If bottled water is unavailable, water should be boiled, which will eradicate *E. histolytica* cysts. Water may be disinfected with iodine or bleach solutions and may also be filtered (References 6, 17).

Table 2. Medications for Amebiasis Infections (References 15, 51)

Infection Type	Medication	Pediatric Dosage (Oral)	Dosage Forms	Common Adverse Drug Reactions	Comments
Asymptomatic or intraluminal	Iodoquinol	30–40 mg/kg/day divided every 8 hours for 20 days (max dose 1.95 g/day)	Tablet: 210 mg, 650 mg	Pruritis, urticaria, diarrhea, nausea, headache	Tablets may be crushed and mixed with applesauce or chocolate syrup.
	Paromomycin	25–35 mg/kg/day divided every 8 hours for 7 days (max dose 4 g/day)	Capsule: 250 mg	Abdominal cramping, diarrhea, nausea	
Dysentery[a]	Metronidazole	35–50 mg/kg/day in divided doses every 8 hours for 10 days (max dose 2.25 g/day)	Capsule: 375 mg Tablet: 250 mg, 500 mg	Nausea, headache	May need to compound oral suspension 50 mg/mL (Reference 12).
Extraluminal[a]	Metronidazole	35–50 mg/kg/day in divided doses every 8 hours for 7–10 days (max dose 2.25 g/day)		Nausea, headache	May need to compound oral suspension 50 mg/mL (Reference 12).
	Tinidazole	50 mg/kg/day for 3–5 days (max dose 2 g/day)	Tablet: 250 mg, 500 mg	Nausea, altered sense of taste	Only in children > 3 years Take with food. Oral suspension 67 mg/mL can be compounded (Reference 13).

[a]After completion of treatment for dysentery or extraluminal disease, patients should be treated with an intraluminal medication (paromomycin or iodoquinol) to clear the intestinal organisms.

Systemic Protozoa

Malaria

Malaria is a significant cause of morbidity and mortality in developing nations worldwide, with around 2 million deaths per year, mostly in children younger than 5 years (Reference 19). Although uncommon in the United States, 1484 cases of malaria in the United States in 2009 were passively reported to the CDC, including four deaths (Reference 22). Most of these cases occurred in individuals who had traveled to endemic areas and did not adhere to chemoprophylaxis guidelines. Most of the other cases were seen in immigrants and visitors from endemic areas. In 2009, 16% of cases in the United States occurred in children younger than 18 years, accounting for 225 children total, mainly between age 2 and 17 years (Reference 22). Most of these infections were attributed to travel to Africa, and only 31% of those infected reported having taken chemoprophylaxis (Reference 22).

Malaria is caused by four different species of the *Plasmodium* parasite: *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae* (Reference 21). Presentation in humans is similar in all four species and can make it difficult to differentiate during diagnosis, but of these, *P. falciparum* is the most deadly. *P. vivax* and *P. ovale*, though not often fatal, are responsible for significant morbidity in endemic areas and may lie dormant in liver hepatocytes for months to years after exposure (Reference 21). *P. vivax* is endemic to India, Pakistan, Bangladesh, Sri Lanka, and Central America, and it has the greatest burden of disease with a long incubation period but rarely causes severe complications. *P. falciparum* is endemic in Africa, Haiti, the Amazon region, the Dominican Republic, and New Guinea, and infected individuals may progress to life-threatening illness within hours of infection (Reference 23). *P. malariae* has worldwide distribution and often manifests with proteinuria. *P. ovale* infections mainly occur in Africa, and infections are usually less severe and relapse less often; spontaneous recovery is not uncommon (Reference 24).

Transmission of malaria occurs when an infected female *Anopheles* mosquito bites a human host. During the blood meal, the mosquito injects sporozoites of *Plasmodium* spp. into the bloodstream of the victim (Reference 24). These sporozoites travel to the liver, where asexual reproduction of the parasites enters a latent stage that lasts between 8 and 30 days (Reference 21). *P. vivax* and *P. ovale* form dormant hypnozoites that will remain in the liver unless targeted therapy is administered. Without directed therapy to these dormant hypnozoites, a relapsing form of the disease can occur. After the latent stage, merozoites, or daughter cells, are released from the liver back into systemic circulation. The merozoites infect erythrocytes and begin another asexual reproductive cycle that results in the lysing of the red blood cells within 2–6 days (Reference 21).

Initial presentation of malaria may involve nonspecific symptoms such as fever, chills, malaise, diaphoresis, vomiting, and rigors (References 21, 24). Patients may experience headache, myalgia, abdominal pain, arthralgia, and cyclic shivering and sweating. Anemia and splenomegaly may develop because of the extensive hemolysis seen during the erythrocytic phase of infection. The most severe complications, including hypoglycemia, thrombocytopenia, acute renal failure, heart failure, seizures, and coma, are seen in patients infected with *P. falciparum* because of its ability to invade erythrocytes of all ages, resulting in high levels of parasitemia (Reference 25). Patient groups at highest risk of these complications from *P. falciparum* are children younger than 5 years and pregnant women (Reference 20). Most young children will become restless or drowsy and experience loss of appetite, persistent fever, flulike symptoms, seizures, vomiting, and/or diarrhea (References 26, 27). Typically, young children do not exhibit the cyclic shivering and sweating, but older children may. Neonates who exhibit signs and symptoms of parasitemia within 1 week of birth contract malaria through transplacental transmission and have congenital malaria. They often present with fever and poor feeding in addition to objective findings of anemia, hepatosplenomegaly, and jaundice (References 26, 28).

The gold standard for diagnosing malaria is the detection of parasites on blood smear by light microscopy (Reference 22). Blood smears should be obtained every 12–24 hours on 3 consecutive days; a positive finding indicates infection (Reference 21). Diagnosis of malaria can be difficult in children because only 50% who are infected will have a positive blood smear, even with repeated examinations. Blood antigen capture tests have a high sensitivity and specificity and can produce rapid results. Both DNA and RNA probes as well as polymerase chain reaction (PCR) also have good sensitivity and specificity and may be used to confirm a diagnosis (References 21, 24).

Pharmacotherapy for malaria can be grouped into two categories: chemoprophylaxis for travelers to endemic areas and treatment of the active infection. The goal of chemoprophylaxis is to lessen the likelihood of transmission because no preventive regimen is 100% effective. The goals of care are to quickly and effectively identify the infecting *Plasmodium* spp. and eradicate the infection to avoid complications.

Prevention

Prevention of malaria infection should consist of a combination of mosquito avoidance measures and chemoprophylaxis. Malarial transmission usually occurs between dusk and dawn in endemic areas, secondary to the feeding habits of the *Anopheles* mosquito. Contact with mosquitos may be reduced by wearing clothes that cover most areas of the body, remaining in well-screened areas, using mosquito bed nets, and using a pyrethroid-containing insect spray in both living and sleeping areas, especially during evening and nighttime hours (Reference 29). Children older than 2 months should have a DEET-containing spray (*N, N*-diethyl-meta-toluamide) of up to 50% applied to exposed parts of the skin when mosquito exposure is expected. The CDC also recommends the use of a permethrin-containing product for application to clothes and bed nets as additional protection (Reference 29).

Before choosing a chemoprophylaxis regimen, several patient-specific factors should be considered, including other medical conditions, concurrent medications, and potential adverse effects of the antimalarial medication (Reference 29). All chemoprophylaxis regimens involve taking a medication before, during, and after leaving the endemic area (Reference 29). It is vital that a thorough assessment of the travel plan with respect to location and any known information on the area's transmission rates and antimalarial drug resistance patterns occur well in advance of departure. An excellent resource on endemic area transmission rates and resistance is the CDC *Yellow Book on Traveler's Health*, which is updated regularly and available online at wwwnc.cdc.gov/travel/page/yellowbook-2012-home.htm. Another helpful resource is the World Health Organization International Travel Web site at www.who.int/ith/en/.

All pediatric patients are at high risk of complications and transmission of malaria. Children traveling to endemic areas should be taking prophylactic antimalarial medications (Table 3). Depending on the incidence of drug resistance at the destination, chloroquine and mefloquine are good options. *P. falciparum* is chloroquine resistant in most endemic areas, except for Central America, including Mexico, the Caribbean, and some countries in the Middle East (Reference 29). In areas where *P. falciparum* is resistant, mefloquine is an alternative option. Children traveling to areas where *P. vivax* is predominant may use primaquine, provided they are not G6PD (glucose-6-phosphate dehydrogenase)-deficient (Reference 29). Doxycycline is an option for use in children older than 8 years in chloroquine- or mefloquine-resistant malaria areas (References 21, 29).

Unfortunately, antimalarial drugs available in the United States come only in tablet form, and the taste can be quite bitter. If the child cannot swallow tablets, a compounding pharmacy may be able to produce an appropriate extemporaneous liquid formulation. Alternatively, the caregiver can crush and mix the tablet with a small amount of applesauce or syrup to ensure that the entire dose is delivered to the child.

Treatment

Treatment strategies depend on the species of malaria, drug resistance patterns in the area where the infection was acquired, age, pregnancy status, and disease severity (Reference 29). Medications used for the treatment of malaria are active against the erythrocyte attack phase. Chloroquine, quinine, quinidine, mefloquine, doxycycline, atovaquone/proguanil, and artemether/lumefantrine are used for treatment. *P. vivax* and *P. ovale* have dormant stages in the liver, and their treatment regimens must include primaquine to eradicate these forms to prevent disease relapse (Table 4).

Children who are exhibiting fever yet able to maintain adequate hydration and nutrition can be treated as outpatients. Acetaminophen can be used for the treatment of fever at 10–15 mg/kg/dose orally every 4–6 hours. Although many children with malaria develop anemia, transfusions with packed red blood cells are rarely needed. Any child with vomiting, signs of dehydration, altered consciousness, convulsions, or difficulty breathing should be admitted to the hospital for treatment and supportive care.

Patients treated with antimalarial therapy should be monitored for resolution of symptoms. Unfortunately, prior malarial infection does not necessarily produce immunity in patients, and research has not yet provided an effective vaccine. Health care providers should stress the importance of prophylactic measures for any travelers to malaria-endemic areas.

Trypanosomiasis (Chagas Disease)

Chagas disease is caused by infection with *Trypanosoma cruzi*, a protozoan parasite carried by Reduviid bugs, which are also known as cone-nosed bugs or kissing bugs because of their propensity to feed at night, usually on an uncovered face (Reference 32). Infection occurs when the bug defecates while feeding, and fecal material containing *T. cruzi* is introduced into the host through the bite or through mucous membranes (Reference 33). Other methods of transmission are blood transfusion, congenital transfer from mother to fetus, or ingestion of food or water contaminated with bug feces (Reference 32). Reduviid bugs live in the wall cracks of houses in rural areas of Central and South America, and it is estimated that 10 million people worldwide are

Table 3. Prophylactic Antimalarial Medications (References 15, 21, 29, 52)

Medication	Dosage	Dosage Forms Available	Duration	Common Adverse Drug Reactions
Chloroquine	5 mg/kg base once weekly (max dose 300 mg base)	Tablet: 250 mg (150 mg base), 500 mg (300 mg base)	Start 2 weeks before and continue for 4 weeks after exposure. Suspension (compounded): 15 mg/mL (9 mg base/mL) (Reference 30)	Nausea, abdominal pain, diarrhea, blurred vision
Chloroquine-Resistant Areas				
Atovaquone/ proguanil	5–8 kg: 31.25 mg/12.5 mg once daily 9–10 kg: 46.88 mg/18.75 mg once daily 11–20 kg: 62.5 mg/25 mg once daily 21–30 kg: 125 mg/50 mg once daily 31–40 kg: 187.5 mg/75 mg once daily > 40 kg: 250 mg/100 mg once daily	Pediatric tablet: atovaquone 62.5 mg/ proguanil 25 mg Tablet: atovaquone 250 mg/proguanil 100 mg	Start 2 days before and continue for 1 week after exposure. Tablet may be crushed or chewed.	Photosensitivity, pruritis, abdominal pain, diarrhea, nausea, changes in liver function, headache, cough
Doxycycline[a]	2 mg/kg once daily (max dose 100 mg/day)	Tablet: 50 mg, 100 mg Capsule: 50 mg, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL	Start 2 days before and continue for 4 weeks after exposure.	Photosensitivity, diarrhea, nasopharyngitis
Mefloquine	≤ 9 kg: 5 mg/kg once weekly 10–19 kg: ¼ tablet once weekly (62.5 mg) 20–30 kg: ½ tablet once weekly (125 mg) 31–45 kg: ¾ tablet once weekly (187.5 mg) > 45 kg: 1 tablet once weekly (250 mg) (max dose 250 mg/week)	Tablet: 250 mg	Start 1 week before and continue for 4 weeks after exposure. Take with food.	Abdominal pain, diarrhea, nausea, vomiting, bradycardia
Primaquine	0.5 mg/kg base once daily (max dose 30 mg base/day)	Tablet: 26.3 mg (15 mg base)	Start 2 days before and continue for 1 week after exposure.	Abdominal pain, nausea

[a]Only for use in children ≥ 8 years.

infected with *T. cruzi* (Reference 15). Most individuals infected with *T. cruzi* in the United States are immigrants from endemic areas of Latin America, but seven vector-borne cases have been reported in the United States since 1995 (Reference 33).

The clinical course of Chagas disease consists of two phases: acute and chronic. The acute phase in adults is mostly asymptomatic, but children are more likely to exhibit a red nodule at the site of inoculation within 1 week of infection (Reference 15). If the inoculation site is the eye, unilateral orbital edema may result, also known as the Romaña sign. This is followed by fever, malaise, hepatosplenomegaly, and lymphadenopathy (References 15, 34). Complications from acute infection may include myocarditis and meningoencephalitis (Reference 35). The acute phase usually lasts between 4 and 8 weeks, after which the parasitic load drops to undetectable levels, and is then followed by asymptomatic chronic infection (References 36, 37).

Most patients who are infected will never develop symptoms but will remain infected throughout their lives (Reference 37). However, 20% to 30% (mostly adults with long-standing disease) will develop manifestations of chronic Chagas disease, including cardiac aneurysms, megaesophagus, and megacolon. Infected mothers may pass the infection to their infants. In the United States, it is estimated that between 65 and 315 congenital *T. cruzi* infections occur annually (Reference 33). Most infected

Table 4. Treatment of Malaria (*P. falciparum* or unidentified species) (References 21, 29, 53)

Medication	Pediatric Dosage (Oral)	Dosage Forms Available	Comments
Chloroquine Sensitive (Uncomplicated)			
Chloroquine	10 mg base/kg, followed by 5 mg base/kg at 6, 24, and 48 hours Total dose = 25 mg base/kg	Tablet: 250 mg (150 mg base), 500 mg (300 mg base)	Do not exceed 600 mg base for first dose and 300 mg base for subsequent doses. Suspension (compounded): 15 mg/mL (9 mg base/mL) (Reference 30) Common ADR: nausea, abdominal pain, diarrhea, blurred vision
Hydroxychloroquine	10 mg base/kg, followed by 5 mg base/kg at 6, 24, and 48 hours Total dose = 25 mg base/kg	Tablet: 200 mg (155 mg base)	Do not exceed 620 mg base for first dose and 310 mg base for subsequent doses. Suspension (compounded): 25 mg/mL (19.4 mg base/mL) (Reference 31) Common ADR: headache, abdominal pain, nausea, corneal disorders
Chloroquine Resistant[a] *(Uncomplicated)*			
Artemether/ lumefantrine	From 5 to < 15 kg: 1 tablet per dose From 15 to < 25 kg: 2 tablets per dose From 25 to < 35 kg: 3 tablets per dose ≥ 35 kg: 4 tablets per dose	Tablet: 20 mg of artemether/ 120 mg of lumefantrine	3-day treatment totals six oral doses: initial dose, followed by second dose in 8 hours; then one dose twice daily for the next 2 days Common ADR: diarrhea, vomiting, headache, cough, fever
Atovaquone/proguanil	5–8 kg: 2 pediatric tablets daily for 3 days 9–10 kg: 3 pediatric tablets daily for 3 days 11–20 kg: 1 adult tablet daily for 3 days 21–30 kg: 2 adult tablets daily for 3 days 31–40 kg: 3 adult tablets daily for 3 days > 40 kg: 4 adult tablets daily for 3 days	Pediatric tablet: atovaquone 62.5 mg/ proguanil 25 mg Adult tablet: atovaquone 250 mg/ proguanil 100 mg	May cause photosensitivity reactions Common ADR: pruritis, abdominal pain, diarrhea, nausea, changes in liver function, headache, cough
Mefloquine	13.7 mg base/kg for first dose, followed by 9.1 mg base/kg given 6–12 hours after initial dose Total dose = 22.8 mg base/kg (max dose = 1250 mg or 1140 mg base)	Tablet: 250 mg (228 mg base)	Take with food. Common ADR: abdominal pain, diarrhea, nausea, vomiting, bradycardia

(continued)

Table 4. Treatment of Malaria (*P. falciparum* or unidentified species) (References 21, 29, 53) *(continued)*

Medication	Pediatric Dosage (Oral)	Dosage Forms Available	Comments
Quinine sulfate + one of the following: doxycycline, tetracycline, or clindamycin[b]	Quinine: 10 mg/kg every 8 hours for 3–7 days[c] Doxycycline: 2.2 mg/kg every 12 hours for 7 days Tetracycline: 25 mg/kg/day divided every 6 hours for 7 days Clindamycin: 20 mg/kg/day divided every 8 hours for 7 days	Quinine sulfate: capsule 324 mg Doxycycline: tablet: 50 mg Capsule: 50 mg, 100 mg Suspension: 25 mg/5 mL Syrup: 50 mg/5 mL Tetracycline: capsule: 250 mg, 500 mg Clindamycin: capsule: 75 mg, 150 mg, 300 mg Solution (oral): 75 mg/5 mL	Doxycycline and tetracycline should not be used in children younger than 8 years. Common ADR Quinidine: syncope, photosensitivity, rash, diarrhea, nausea, vomiting, loss of appetite
Severe Malaria[c,d] *(Complicated)*	Intravenous Therapy		
Quinidine gluconate + one of the following: doxycycline, tetracycline, or clindamycin	Quinidine gluconate: 6.25 mg base/kg loading dose IV over 1–2 hours; then 0.0125 mg base/kg/minute infusion for at least 24 hours: once parasite density is less than 1% and patient can take oral medications, change to quinine oral dosing as above[c] Doxycycline: 2.2 mg/kg IV every 12 hours (< 45 kg), or 100 mg IV every 12 hours (≥ 45 kg) for 7 days. Change to oral dosing as above when able. Tetracycline: 25 mg/kg/day orally divided every 6 hours for 7 days Clindamycin: 10 mg/kg IV loading dose, followed by 5 mg/kg IV every 8 hours for 7 days. Change to oral dosing as above when able.	Quinidine gluconate: IV: 80 mg/mL (base 50 mg/mL) Doxycycline: IV: 100 mg of powder for reconstitution Clindamycin: IV: 150 mg/mL	During administration of quinidine, monitor for hypotension, hypoglycemia, and cardiac changes. Doxycycline and tetracycline should not be used in children younger than 8 years. Common ADR Quinidine: syncope, photosensitivity, rash, diarrhea, nausea, vomiting, loss of appetite

[a]Treatment with atovaquone/proguanil, artemether/lumefantrine, or quinine + doxycycline, tetracycline, or clindamycin is equally recommended. Mefloquine should only be used when there are contraindications to the other preferred treatments because of severe neuropsychiatric reactions seen with mefloquine at treatment doses.
[b]Quinine in combination with doxycycline or tetracycline is generally preferred to combination with clindamycin because of better efficacy data.
[c]Infections acquired in Southeast Asia should receive quinine/quinidine for 7 days; all others should continue for 3 days.
[d]Patients with a diagnosis of severe malaria should be aggressively treated with parenteral antimalarial therapy. Intravenous quinidine should be initiated as soon as diagnosis is confirmed. Consultation with a physician experienced in treating malaria and a cardiologist is recommended. Severe cardiac complications with quinidine may require temporary discontinuation of the drug or a decrease in the intravenous infusion rate.
ADR = adverse drug reactions; IV = intravenous(ly)

newborns are asymptomatic, or they may have nonspecific symptoms such as low birth weight, low Apgar scores, prematurity, anemia, or thrombocytopenia (Reference 36). Although serious complications, such as myocarditis, meningoencephalitis, and respiratory disease, are rare in newborns, they carry a high risk of mortality (Reference 36). Before 2007, when widespread blood bank screening in the United States was initiated, it was possible to contract *T. cruzi* from infected donated blood products (Reference 32). From 1993 to 2007, five transfusion-related cases were documented in the United States, all occurring in immunocompromised individuals (Reference 32). Reactivation of disease and symptoms may occur in chronically infected individuals who become immunocompromised (Reference 37).

Diagnosis of acute trypanosomiasis is made through microscopic examination of the blood for the presence of the parasite. Suspected cases of chronic trypanosomiasis infection should be evaluated through serologic testing for antibodies to *T. cruzi*. Because the available assays may yield low sensitivity and/or specificity rates, WHO Chagas experts recommend that each specimen be tested with two types of assays, such as ELISA (enzyme-linked immunosorbent assay), IIF (indirect immunofluorescence), or indirect hemagglutination (References 34, 37).

The goals of therapy for treating acute and congenital *T. cruzi* infections are to reduce disease duration and prevent chronic infection. Two medications have proven efficacy against *T. cruzi*: nifurtimox and benznidazole. Although neither drug is FDA labeled for use in the United States, each may be obtained directly from the CDC under investigative protocols. Drug treatment is always recommended for acute and reactivated *T. cruzi* infections in individuals of all ages, in early congenital infections, and in children younger than 18 years with chronic *T. cruzi* infection (References 32, 37). If treatment is initiated in the acute phase of infection, the parasitologic cure rate is about 85%, and it is about 90% in congenitally infected infants treated in the first year of life (Reference 36). In children younger than 18 years with chronic asymptomatic disease, benznidazole has shown 60% efficacy in attaining cure and appears to slow the development and progression of Chagas cardiomyopathy in chronically infected older children and adults (Reference 36). Benznidazole is typically given for 60 days and nifurtimox for a 90-day course of therapy. In children younger than 12 years, benznidazole should be dosed at 5 mg/kg orally twice daily, and for those 12 years and older, the dose is 2.5–3.5 mg/kg orally twice daily. Common adverse effects include anorexia and weight loss, allergic dermatitis, peripheral neuropathy, and insomnia. Dosing for nifurtimox in children 10 years or younger is 5–6.5 mg/kg orally three times/day; for those 11–16 years of age, 4–5 mg/kg orally three times/day; and for those 17 years and older, 2.5–3 mg/kg orally three times/day. Common adverse effects of nifurtimox include anorexia, weight loss, nausea, vomiting, headache, dizziness, vertigo, and polyneuropathy. Both drugs are contraindicated in severe hepatic and/or renal disease and in breastfeeding (Reference 37). Treatment efficacy can be assessed through monitoring for the disappearance of *T. cruzi*–specific antibodies, although antibody disappearance may take up to several years in some patients. Treatment failures can be assessed by repeated hemoculture or PCR-based assay (Reference 37).

Preventive measures of infection should include the use of insecticides in the sleeping areas of infested houses. Travelers to endemic areas are rarely at risk, but if they will be camping, sleeping outdoors, or sleeping in houses with poor construction, the use of insecticide-impregnated bed nets is recommended (Reference 37).

Toxoplasmosis

Toxoplasma gondii exists worldwide in animals and birds, although felines are the most common source (Reference 15). Oocytes of *T. gondii* can survive in moist soil for up to 18 months; however, their survival is decreased in dry, extremely cold or hot climates and at higher altitudes. Human infection may occur through the ingestion of food or water that is contaminated with infected cat feces; through the ingestion of undercooked infected animal meats from cattle, sheep, or pigs containing *T. gondii* sporozoites; or congenitally from an infected mother to fetus (References 38, 39). Congenital toxoplasmosis occurs in around 500–5000 newborns per year in the United States (Reference 40). In most cases in children and adults, infection is asymptomatic and will resolve spontaneously without treatment; however, treatment is indicated for pregnant mothers, neonates, and immunocompromised individuals (Reference 15).

Cats become infected with toxoplasmosis by eating infected birds, rodents, or other small animals. Sporozoites, which are eliminated in cat feces, must undergo sporulation to become infectious, which usually takes 2–3 days in temperate climates. Cats may shed 1–100 million sporozoites up to 3 weeks after their first infection. The risk of infection from cat litter boxes may be minimized if the litter is changed daily before this process occurs (Reference 40). Human infection results from ingesting contaminated or inadequately cooked food infected with tissue cysts or sporozoites. It is theorized that flies and cockroaches transport sporozoites to water and food. Once infected, only 10% to 20% of acute infections produce symptoms, of which the most common is lymphadenopathy without fever (Reference 38). Other physical findings may include fever, malaise, myalgia,

hepatosplenomegaly, and lymphocytosis. Toxoplasmosis in immunocompetent individuals is self-limited, though lymphadenopathy may persist for a few months (Reference 38). In immunocompromised hosts, such as those undergoing chemotherapy for malignancy, those with human immunodeficiency virus (HIV), or those who take immunosuppressive medications posttransplant, severe toxoplasmosis can follow acute infection or reactivation of prior infection (Reference 38). Severe toxoplasmosis can lead to complications such as encephalitis, chorioretinitis, myocarditis, or pneumonia. Pregnant women who are infected are of special concern because they may pass the infection to their baby. Infection early in pregnancy may result in fetal demise, miscarriage, or severe congenital effects in the infant, whereas infection in the later stages of pregnancy is more likely to be associated with vertical transmission to the baby (Reference 15). Although most neonates are asymptomatic at birth, symptoms may include fever, microcephaly or hydrocephaly, hepatosplenomegaly, jaundice, chorioretinitis and/or blindness, seizures, intracranial calcifications, myocarditis, strabismus, thrombocytopenia, and an erythroblastosis-like syndrome (Reference 41). The overall mortality rate of congenital toxoplasmosis is around 10%, and newborns with acute symptoms often die within the first month of life (Reference 42).

Toxoplasmosis is diagnosed by the identification of *Toxoplasma*-specific IgG, IgM, or IgA (immunoglobulin G, M, and A) antibodies, either through indirect fluorescent antibody test or enzyme immunoassays. Direct observation of the parasite in biopsy tissue is also diagnostic (Reference 39). In pregnant women, PCR can be performed on amniotic fluid at 18 weeks' gestation (Reference 43).

The treatment goal is to eradicate the rapidly dividing parasitic organisms in acute infection. Treatment may not be needed in patients who are immunocompetent with acute infection because the infection is usually self-limited. Treatment of existing acute infection will not reverse central nervous system damage that is already present, but it may prevent further sequelae. Treatment of infected pregnant women may reduce vertical transmission to the fetus and the frequency of adverse outcomes (Reference 38).

Children who are immunocompetent with toxoplasmic lymphadenopathy should not be treated unless the symptoms are severe because the disease is usually self-limited. Immunocompromised patients should receive a three-drug regimen of pyrimethamine with sulfadiazine plus leucovorin to prevent hematologic toxicity. Patients who are allergic to or cannot tolerate sulfadiazine can use clindamycin instead (Table 5). Alternative therapy with trimethoprim/sulfamethoxazole may be used, but it may not be as active in immunocompromised patients (Reference 38).

Pregnant women with acute toxoplasmosis should receive spiramycin 3 g orally three times daily without food until term or until fetal infection has been documented (Reference 38). If fetal infection is documented after 18 weeks' gestation, the three-drug regimen of pyrimethamine with sulfadiazine plus leucovorin should be initiated and continued until term (References 34, 40). Because pyrimethamine has teratogenic effects, it cannot be used during the first trimester of pregnancy (References 38, 47).

Neonates and infants with congenital toxoplasmosis should be treated for 1 year with pyrimethamine and sulfadiazine plus leucovorin, though treatment practices may vary by neonatal center (References 38, 41). Treatment is generally discontinued when blood tests are negative for *Toxoplasma* antibodies (Reference 41).

Prevention of toxoplasmosis includes proper handwashing techniques, especially for pregnant women and immunocompromised individuals. Hands should be thoroughly washed after handling raw meat and unwashed vegetables and fruits. Cutting boards, dishes, counters, and utensils should be washed in hot, soapy water after contact with raw meat. To limit environmental exposure, gloves should be worn when gardening or coming into contact with dirt or sand because hands may be contaminated with infected cat feces. Cat litter boxes should be changed daily but not by pregnant or immunocompromised individuals. To decrease transmission from cats, they should be kept indoors and fed only canned or dried commercial foods. All outdoor sandboxes should be covered when not in use (Reference 47).

Helminths

Ascariasis

Infection with the parasite *Ascaris lumbricoides*, the largest intestinal nematode found in humans, is distributed worldwide, but it is more common in Southeast Asia, Africa, and South and Central America, with more than 1.4 billion individuals infected worldwide (Reference 48). In the United States, 4 million are thought to be infected. Most are immigrants from endemic countries. The southwestern states and those along the Gulf of Mexico were once endemic areas (Reference 49). Although most cases are asymptomatic, morbidity is related to worm burden. Intestinal obstruction is the most common complication, followed by bile duct obstruction, gastrointestinal perforation, peritonitis, and volvulus (Reference 50). Children aged 1–5 years are most likely to have intestinal obstruction, and all children are likely to have malnutrition, leading to growth retardation, cognitive impairment, and poor academic performance (References 50, 51). Some studies have linked *Ascaris* infection with an increased risk of allergic diseases and asthma, although this is controversial (References 51, 52).

Table 5. Medications for Toxoplasmosis in Pediatrics and Pregnancy (References 15, 38, 47, 56)

Infection Type	Medication	Dosage (Oral)	Dosage Forms (Oral)	Common Adverse Drug Reactions
Immunocompetent, nonsevere	No treatment needed			
Immunocompromised (not patients with HIV)	Pyrimethamine	2 mg/kg/day for 2 days; then 1 mg/kg/day for 4 weeks (max dose = 25 mg/day)	Tablet: 25 mg Suspension (compounded): 2 mg/mL (Reference 44)	Rash
	Sulfadiazine	50 mg/kg every 6 hours for 4 weeks (max dose = 6 g/day)	Tablet: 500 mg Suspension (compounded): 200 mg/mL (Reference 45)	Rash, abdominal pain, diarrhea, nausea
	Leucovorin	10–25 mg given with pyrimethamine	Tablet: 5 mg, 10 mg, 15 mg, 25 mg Suspension (compounded): 5 mg/mL (Reference 46)	Diarrhea, nausea, stomatitis, fatigue
Alternative	TMP/SMX	TMP 5 mg/kg, SMX 25 mg/kg twice daily for 4 weeks	Tablet: 400 mg SMX/80 mg TMP, 800 mg SMX/160 mg TMP Suspension: 200 mg SMX/40 mg TMP per 5 mL	Rash, urticaria, nausea, loss of appetite
	Clindamycin	5–7.5 mg/kg four times daily (max dose = 1.8 g/day)	Capsule: 75 mg, 150 mg, 300 mg Solution: 75 mg/5mL	Rash, abdominal pain, diarrhea, nausea
Acute toxoplasmosis in pregnancy	Spiramycin	3 million units (1 g) every 8 hours	Not commercially available in United States: may obtain through FDA with an IND, after consultation[a]	Rash, abdominal pain, nausea, blurred vision
Fetal infection after 18 weeks' gestation	Pyrimethamine	50 mg twice daily for 2 days; then 50 mg once daily to term	Tablet: 25 mg Suspension (compounded): 2 mg/mL	Rash
	Sulfadiazine	37.5 mg/kg twice daily for 2 days; then 50 mg/kg twice daily to term (max dose = 4 g/day)	Tablet: 500 mg Suspension (compounded): 200 mg/mL	Rash, abdominal pain, diarrhea, nausea
	Leucovorin	5–20 mg/day during treatment and for 1 week after pyrimethamine	Tablet: 5 mg, 10 mg, 15 mg, 25 mg Suspension (compounded): 5 mg/mL	Diarrhea, nausea, stomatitis, fatigue
Congenital toxoplasmosis in neonates and infants[b]	Pyrimethamine	2 mg/kg/day for 2 days; then 1 mg/kg/day for 6 months; then three times/week for 1-year total treatment (max dose = 25 mg/day)	Tablet: 25 mg Suspension (compounded): 2 mg/mL	Rash
	Sulfadiazine	50 mg/kg twice daily for 1 year (max dose = 6 g/day)	Tablet: 500 mg Suspension (compounded): 200 mg/mL	Rash, abdominal pain, diarrhea, nausea
	Leucovorin	10 mg three times/week during treatment and for 1 week after pyrimethamine	Tablet: 5 mg, 10 mg, 15 mg, 25 mg Suspension (compounded): 5 mg/mL	Diarrhea, nausea, stomatitis, fatigue

[a]Palo Alto Medical Foundation Toxoplasma Serology Laboratory, telephone (650) 853-4828; or U.S. National Collaborative Trial Study, telephone (773) 834-4152.
[b]Practice varies between centers.
HIV = human immunodeficiency virus; IND = investigational new drug; TMP/SMX = trimethoprim/sulfamethoxazole.

A. lumbricoides is acquired through the ingestion of embryonated eggs, which hatch in the jejunum and release larvae that penetrate the intestinal wall and enter the portal venous circulation, migrating to the liver. From the liver, the larvae migrate to the lungs through the venous circulation, break into the alveolar spaces, ascend to the tracheobronchial tree, and pass the epiglottis, where they are swallowed. They return to the jejunum and mature into adult worms. The adult worms can live for 1–2 years and are capable of producing 240,000 eggs per day. The elapsed time from initial ingestion to the development of mature adults is 18–24 days (References 48, 50, 53). Eggs are excreted in feces, where they complete embryonization while in the soil (Reference 50). Mature female worms are from 20 to 40 cm long, whereas male worms may be between 12 and 25 cm (Reference 50). Adult worms move through the gastrointestinal tract and can move in and out of the biliary tract, pancreas, appendix, and diverticula, where they may create obstruction and cause inflammation, necrosis, infection, and abscess formation (Reference 48).

In most cases, individuals are asymptomatic but may exhibit anorexia, abdominal discomfort, and diarrhea. In children, the most common complication is intestinal obstruction secondary to an entangled worm bolus. Symptoms include sharp, colicky abdominal pain; fever; diarrhea; and vomiting. The vomitus may contain worms. Severely malnourished children may progress to sepsis and septic shock. Pulmonary ascariasis symptoms, which may develop 1–2 weeks after infection, are rarely life threatening, but they may include chest pain, dry cough, fever, dyspnea, and wheezing. However, most children with pulmonary ascariasis are asymptomatic (References 49, 50).

Diagnosis can be made by a microscopic examination of the feces for eggs. Adult worms may be coughed out or passed through the rectum. Eosinophilia may be evident, especially in the lung migration phase, and can be profound in pulmonary ascariasis cases. Abdominal ultrasonography is useful for identifying worms in the biliary tree (Reference 49).

The goal of therapy is to eradicate the worms from the intestinal tract; however, antihelminthic medications are not recommended in patients with large worm burdens and abdominal pain because of the risk of precipitating intestinal obstruction as the worms die. The drugs of choice are pyrantel pamoate, albendazole, and mebendazole, which have efficacy rates of 88%, 95%, and 88%, respectively (Reference 54) (Table 6). For both children and adults, the treatment course may be repeated if there is no cure within 3–4 weeks. In symptomatic pregnant women, the drug of choice is pyrantel pamoate, which should only be used when the patient's active symptoms have subsided (Reference 55).

Children receiving any of these medications for eradication of ascariasis should be monitored for adverse reactions, which are rare with short-term use. Pyrantel pamoate should be used with caution in patients with existing liver dysfunction. Patients with phenylketonuria should avoid the use of the chewable tablet, which contains aspartame. Some suspensions of pyrantel pamoate contain sodium benzoate, a metabolite of benzyl alcohol, which has been associated with gasping syndrome in neonates if administered in large amounts. Although it is unlikely that excessive amounts would be reached when treating ascariasis in neonates, caution is warranted. Other adverse effects in children taking pyrantel pamoate include gastrointestinal upset, nausea, diarrhea, abdominal cramps, headache, and rash. Albendazole should be used with caution in patients with abnormal liver function tests and in patients with a decreased leukocyte count. Other adverse effects include rash, urticaria, headache, abdominal pain, nausea, and vomiting. Adverse reactions with mebendazole include gastrointestinal effects such as nausea, vomiting, diarrhea, and abdominal pain. Rash, pruritus, and headache also occur (Reference 56).

Preventive measures include improvement in sanitation and the practice of good hygiene. In endemic areas, school screenings with subsequent treatment have been beneficial in identifying asymptomatic carriers and improving the health and educational outcomes of school-aged children (Reference 49).

Pinworm

The most common helminth infection in school-aged children in the United States is *Enterobius vermicularis*, or pinworm, with an estimated prevalence of 30% of children (Reference 6). Pinworm, which is found worldwide, especially in temperate regions, occurs in children regardless of socioeconomic level, race, or culture. Humans are the only host of *E. vermicularis*, which does not spread through water or germinate in soil (Reference 57). In addition to school-aged children, other commonly infected groups include adult caretakers of infected children and institutionalized individuals (Reference 58).

Pinworm is transmitted by several methods: finger to mouth, aerogenic, and retroinfection. Fingers become contaminated secondary to scratching in the anal area, and when infected fingers are placed in the mouth (through nail biting, poor hygiene, or inadequate handwashing), autoinfection occurs (Reference 29). Infestation may also occur when eggs adhere to bed linens, soiled clothes, tabletops, and bathroom fixtures; once touched, they stick to fingers or are caught under fingernails. Some research also suggests that pinworm eggs are carried by cockroaches (Reference 59). In aerogenic infestation, eggs are inhaled and ingested from

airborne dust containing eggs that have been dislodged from bed linens and clothes (Reference 57). Retroinfection occurs when a pinworm hatches at the opening to the anus and then reenters the rectum and bowel (Reference 60).

Once the eggs are ingested, the larvae hatch in the duodenum and mature into adult worms within 1–2 months. Adult worms attach to the mucosa of the cecum, appendix, and bowel and live for up to 4–6 weeks (Reference 57). Female pinworms, which are about 5–13 mm long, are threadlike and white. At night, the pregnant female migrates to the anus to deposit as many as 16,000 eggs in the perianal skin. In some cases, worms will migrate into nearby orifices, usually in the female genitourinary tract, leading to symptoms of vulvovaginitis and urinary tract infection (Reference 57). Within 6 hours of being deposited, the eggs become infective and can remain so for up to 14–20 days (Reference 57).

Patients with pinworm infestation will present with perianal and perineal pruritus, which is usually more intense at night as the worms migrate. Some individuals will be asymptomatic, and in rare cases of heavy worm burden, bowel inflammation, perforation, and obstruction may occur. Children may exhibit nausea or abdominal pain, as well as restless sleep, bedwetting, and irritability (Reference 58). Severe itching may lead to anal excoriation and secondary bacterial infection. Infestation with pinworm may also lead to appendicitis (Reference 61).

Diagnosis of pinworm is usually made by a careful clinical history and identification of pinworm eggs from the perianal area using the "tape test." A stool specimen is not very useful because *E. vermicularis* eggs are only detectable in the stool in 5% to 15% of cases (Reference 6). The tape test involves the use of clear adhesive tape to the end of a cotton swab with the sticky side out. The tape should be touched to the areas around the anus in the morning before the child bathes or defecates. The tape should be preserved in a plastic bag and taken to a physician's office for microscopic examination (Reference 57). To reduce false-negative results, this test should be done on 3 consecutive days, which yields a sensitivity of 90% (References 56, 58).

The treatment goal is to eradicate the infestation and reduce morbidity. Several antihelminthic medications are available and are given as two doses, 2 weeks apart. Drugs of choice include pyrantel pamoate, albendazole, and mebendazole (Table 6). Because medications are not completely effective against both eggs and larvae, re-treatment is recommended, which may decrease recurrence rates from 20% to 1% (Reference 62). When treating the patient, all infected household contacts should also be treated with the same agent. Personal hygiene, including changing underclothes daily, good handwashing, and changing bed linens and towels frequently, must be improved, and children should be discouraged from putting their fingers in their mouths (Reference 58). Individuals at risk of infestation should bathe in the morning on awakening to reduce egg contamination (Reference 58).

Patients should be reminded that recurrence is common if the dose is not repeated in 2 weeks. Therapy is much more effective if the patient's household contacts are treated at the same time. Patients should be reexamined after completion of medication therapy to reevaluate for reinfection, especially if perianal itching or pain continues (Reference 58).

Ectoparasites

Pediculosis (Head Lice)

Head lice infestation (pediculosis) is caused by *Pediculus humanus capitis*. In the United States, head lice are most commonly found in school-aged children, especially in preschool and elementary grades, between 3 and 12 years of age (Reference 63). Household members of infested children, as well as other caretakers, may also contract lice. It is estimated that 6–12 million cases of head lice occur annually in the United States (Reference 63). Treatment costs associated with head lice are estimated at $1 billion, and because of "no-nit" policies in U.S. schools, about 12–24 million days of school are lost each year (References 64, 65). Head lice, which are not known to spread disease, are much less common among African Americans (Reference 66).

The adult head louse is about the size of a sesame seed (about 3–4 mm long), whereas the eggs (nits) are much smaller at only 1 mm. A female louse can live 3–4 weeks and lay up to 10 nits daily. Nits are attached to the base of the hair shaft near the scalp with a glue-like substance. Nits need the warmth of body heat to incubate, and in 7–12 days, they hatch, releasing a nymph, which matures during the next 9–12 days to reach the adult stage. Lice feed on blood from the human host every few hours, injecting saliva into the scalp. Mature lice cannot survive for more than 1 day away from the scalp (Reference 63).

Lice are transmitted only by direct close contact. Head-to-head contact is common in young and school-aged children, through play activities, sports, slumber parties, and camp (Reference 66). Less often, lice can be spread through the sharing of clothing such as hats, scarfs, and coats or through sharing of other items that have been in recent contact with the infested person such as combs, brushes, towels, ribbons, and barrettes. Placing the head on a pillow, bed, carpet, or upholstered furniture that has recently been used by an infested person may also promote transmission (Reference 66).

Table 6. Medications for Pediatric Helminth Infections (References 15, 56)

Parasite	Medication	Pediatric Dosage	Dosage Forms	Comments
Ascariasis (*Ascaris lumbricoides*)	Albendazole	400 mg once	Tablet: 200 mg	Tablet may be crushed or chewed.
	Mebendazole	100 mg twice daily for 3 days	Chewable tablet: 100 mg	
	Pyrantel pamoate	11 mg/kg pyrantel base once (max = 1 g)	Suspension: 144 mg/mL (50 mg/mL pyrantel base) Chewable tablet: 720.5 mg (250 mg pyrantel base)	Repeat dose in 2 weeks.
Pinworm (*Enterobius vermicularis*)	Albendazole	400 mg once	Tablet: 200 mg	Repeat dose in 2 weeks.
	Mebendazole	100 mg once	Chewable tablet: 100 mg	Repeat dose in 2 weeks.
	Pyrantel pamoate	11 mg/kg pyrantel base once (max = 1 g)	Suspension: 144 mg/mL (50 mg/mL pyrantel base) Chewable tablet: 720.5 mg (250 mg pyrantel base)	Repeat dose in 2 weeks.

Diagnosis of head lice is made by observation of live lice on the scalp or hair, but this can be difficult. Use of a lice comb or other fine-tooth comb can make this process easier (Reference 67). Nits may be easier to find, especially close to the scalp, but of importance, finding nits does not always confirm that a child is infested. If the nits are found attached to the hair more than ¼ inch from the scalp, they are usually dead or already hatched. Nits can also be confused with dandruff particles or hair debris, but nits are usually difficult to remove from the hair. Although head lice may be found anywhere on the scalp, they are commonly found in the postauricular and occipital areas (Reference 63). Patients may or may not present with pruritus, and many children may be asymptomatic (Reference 66). In some cases, pruritus may lead to excoriations on the scalp and secondary skin infections.

The treatment goal is to eradicate the infestation. Treatment is recommended for all individuals with an active infestation. Nonprescription topical medications, such as 1% permethrin or pyrethrins, can be used as first-line therapy unless there is proven resistance to these products in the community (Table 7). Prescription products such as benzyl alcohol 5% can be used in children older than 6 months, and malathion 0.5% can be used in children older than 2 years. Spinosad 0.9% is a newer topical prescription product that may be used in children 4 years and older. It is ovicidal and does not require the use of a nit comb after use (Reference 68). Topical ivermectin lotion 0.5% may be used to treat head lice infestations in children 6 months and older. Like spinosad, it does not require nit combing after use (Reference 69). These products may also be used when resistance to pyrethrins or permethrin is common or when a patient's nonprescription therapy has failed. If nonprescription treatment is used or if live lice are seen after malathion therapy, product reapplication should occur at the indicated intervals because these products are not completely ovicidal (Reference 63). Lindane, an organochlorine, is only available by prescription and has been reported to cause seizures in children (References 63, 66). The FDA recommends that it be used only for second-line treatment in cases of treatment failure or in those who cannot tolerate other, safer medications. A public health advisory issued by the FDA further emphasized that lindane should not be used in neonates and should be used with extreme caution in all children and individuals who weigh less than 110 lb, who take medications that may lower the seizure threshold, or who are infected with HIV (Reference 63). The state of California has banned the use of lindane, and the American Academy of Pediatrics no longer recommends its use as a pediculicide (Reference 63). If treatment with a pediculicide is contraindicated or parents wish for a nontoxic alternative to pediculicides, "wet-combing" (the use of a fine-tooth comb on wet hair coated with conditioner) can be useful, although it is time-consuming and difficult to perform on active young children. This process should take about 1 hour to complete and should be repeated every 4 days until no more active lice are seen. Another nontoxic option is to employ the use of occlusive products such as petroleum jelly or Cetaphil. Petroleum jelly is massaged into the hair and scalp and left on overnight with a shower cap. This is thought to suffocate the adult louse and block air exchange in the eggs; it may need to be repeated within 2 weeks (Reference 70). Cetaphil is applied to the hair and scalp, dried with a hair dryer, left on overnight, and then washed out in the morning. This process should be repeated once weekly for 3 weeks (Reference 71).

Table 7. Medications for Ectoparasite Infestations (References 56, 63)

Parasite	Medication	Instructions	Comments
Head lice	Permethrin[a] 1%	Topical: Apply to clean, towel-dried hair, leave on for 10 minutes, and rinse with water.	Nonprescription Use in children > 2 months old. May repeat in 1 week if needed.
	Pyrethrin	Topical: Completely wet hair with product, leave on for 10 minutes, wash, and rinse well with warm water.	Nonprescription Repeat in 7–10 days to kill newly hatched lice.
	Benzyl alcohol 5%	Topical: Apply to dry hair. Use enough product to completely saturate hair and scalp. Leave on for 10 minutes, and then rinse well with water. Use fine-tooth comb to remove dead lice and eggs.	Nonprescription For children ≥ 6 months old No ovicidal activity Repeat in 1 week.
	Ivermectin 0.5%	Topical: Apply to dry hair. Use enough product to thoroughly coat the hair and scalp. Leave on for 10 minutes, and then rinse well with water.	Prescription only Use in children ≥ 6 months old Nit combing not required
	Lindane	Topical: Apply 15–30 mL to head and lather for 4 minutes, rinse well, and use fine-tooth comb to remove dead lice and eggs.	Not routinely recommended Last-line therapy Prescription only
	Malathion 0.5%	Topical: Sprinkle product on dry hair and rub in until scalp is moistened. Allow hair to dry naturally. Wash hair after 8–12 hours with a non-medicated shampoo, rinse, and use a fine-tooth comb to remove dead lice and eggs.	Prescription only May repeat application in 7–9 days if needed Contraindicated in neonates and infants
	Spinosad 0.9%	Topical: Apply sufficient amount to cover dry scalp and completely cover dry hair. Leave on for 10 minutes; then rinse thoroughly with warm water.	Prescription only Use in children ≥ 4 years May repeat application in 7 days if live lice seen. Nit combing not required Ovicidal
Scabies	Permethrin[a] 5%	Topical: Apply head to toes, leave on for 8–14 hours, and wash off with water.	Prescription only May reapply in 1 week if live mites present.
	Crotamiton 10%	Topical: Apply to entire body, neck to toes, once daily for 2 days. Bathe 48 hours after last application.	Prescription only May reapply after 7–10 days if mites reappear. In infants and young children, may also apply to neck, head, and scalp; avoid face.
	Ivermectin	Oral: 200 mcg/kg as a single dose for children ≥ 15 kg	Prescription only May repeat dose in 10–14 days
	Lindane	Topical: Apply thin layer to skin from neck to toes. Infants: Wash off 6 hours after application. Children: Wash off 6–8 hours after application.	Not routinely recommended Last-line therapy Prescription only

[a]Drug of choice.

Nit removal is not necessary, but it may be cosmetically desired. Because many schools in the United States have a "no-nit" policy requiring children to be free of nits before returning to school, parents may want to remove nits to avoid confusion. Fine-tooth combs or special "nit combs" are used on wet hair, similar to the "wet-combing" process previously described. Some products claim to loosen the nits from the hair shaft, making the process easier, but no clinical benefit has been shown (Reference 63). Shaving the child's head is very effective in the removal of nits and lice, but it is generally not recommended because of the distress it may cause the child (Reference 63).

Because head lice need a blood meal regularly and do not survive long after they fall off the scalp, aggressive cleaning is not necessary to prevent reinfestation. However, it is recommended that all clothing or washable items that the infested person was in contact with during the 2 days before lice removal treatment be machine washed in hot water and dried on high heat. Because adult lice will not survive long without a blood meal and their eggs typically hatch within 6–10 days, any clothing and items that cannot be washed may be dry-cleaned or tightly sealed in a plastic bag for 2 weeks. All brushes and combs should be washed in hot water for 5–10 minutes. Vacuuming the floor or furniture where an infested person has recently been may be helpful, but the risk of infestation in this circumstance is low (Reference 66).

Scabies

Scabies is caused by infestation with the human itch mite, *Sarcoptes scabiei* var. *hominis*, into the superficial layers of the skin. It can be seen worldwide, and it affects all age groups, races, and social classes. Risk factors for scabies include crowding, especially in poorer socioeconomic settings where lack of proper hygiene exists. Scabies is transmitted through close body contact, and outbreaks often occur in nursing homes, extended care facilities, prisons, and child care facilities (Reference 71).

Scabies mites are transmitted through prolonged direct human contact. The adult female mite is very small, 0.3–0.5 mm long, and can lay as many as 90 eggs after burrowing beneath the stratum corneum for a blood meal. When the female mite burrows, a trail of eggs, debris, and feces is left behind, which induces an immunologic response, manifested by intense pruritus. Larvae hatch under the skin within 3–4 days and mature over 2 weeks into adult mites. In a patient with classic scabies, the average mite population is 10–20 parasites (Reference 72).

The main symptom of scabies is intense, distressing pruritus that worsens at night or with activities that elevate body temperature. Primary lesions include burrows, which look like faint white zigzags on the skin, papules, vesicles, and pustules (References 72, 73). Secondary lesions arise from scratching and may include crusted areas and nodules (Reference 72). In infants, the palms, soles, axillae, and scalp are most commonly affected. In older children, lesions are mostly seen below the neck, including the webbed spaces between the fingers; flexor surfaces of the arms; wrists, and axillae; and waistline. Other affected areas include the umbilicus, penis, nipples, and scrotum (Reference 74). In new infestations, symptoms may take as long as 4–6 weeks to manifest (Reference 73).

A definitive diagnosis of scabies is made by direct visualization of the mites, eggs, or feces in a skin scraping on low-power microscopy (Reference 75). Because this is not always feasible, the diagnosis is often based on clinical signs and symptoms, including the characteristic burrow pattern and history of pruritus that worsens at night.

The goal of therapy is to eradicate the infestation and minimize complications. Treatment of both the infested patient and all close contacts with scabicidal medications is crucial. The drug of choice is permethrin. All scabicidal medications are available only with a prescription, and appropriate application of medication is necessary to ensure successful treatment (Table 7). The medication should be applied to clean skin and left on for the recommended time before washing it off. In older children, the scabicide should be applied to all areas of the body from the neck to the toes, whereas in infants and young children, the head and neck should also be covered. After treatment, clean clothing should be worn. Because the pruritus is typically caused by a hypersensitivity reaction to the mites and their feces, patients may exhibit itching for weeks after treatment, despite killing all mites and eggs. Use of an oral antihistamine or a topical corticosteroid may be helpful to control the itching. Skin sores from itching may become infected and should be treated appropriately with antibiotics (References 72, 73). Patients should be examined 1 month after treatment for complete resolution of signs and symptoms.

All clothing, bedding, and towels used by the infested person should be washed in hot water and dried on the hot setting. Items that are non-washable should be dry-cleaned or placed in a sealed plastic bag and stored for a minimum of 72 hours because scabies mites can live for only 2–3 days without a host. The use of pesticide sprays or fogs is unnecessary (Reference 73).

Conclusions

Parasitic infections in children can have a detrimental effect on a child's well-being, affecting nutritional status, growth, and development. It is vital that clinicians be aware of the signs and symptoms, complications, and available treatment options for the most prevalent parasites, even though they are not as common in the

United States as in other areas of the world. With increasing immigration and travel by children and their families to endemic areas of the world, the impact of parasites in children can be felt in previously unaffected geographic locations in the United States. Public health awareness of transmission risks is important in both the prevention and treatment of parasitic infections in pediatric patients.

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CHAPTER 44

Pediatric Vaccines

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Learning Objectives

1. Classify each of the routine childhood vaccines as a live or inactivated vaccine.
2. Classify each inactivated vaccine as a polysaccharide, conjugate, toxoid, or subunit vaccine.
3. Given a clinical scenario, develop an immunization plan for a child or adolescent.
4. Recognize clinical situations in which a vaccine is contraindicated or should be given with caution.
5. Describe appropriate methods to minimize vaccine-related adverse events.
6. Identify reliable electronic references for current vaccine information.

Abbreviations in This Chapter

DTaP	Pediatric vaccine containing diphtheria and tetanus toxoids and acellular pertussis vaccine
Hib	*Haemophilus influenzae* type b
HPV	Human papillomavirus
MMR	Measles, mumps, and rubella vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
Td	Adolescent and adult tetanus toxoid and reduced diphtheria toxoid vaccine
Tdap	Adolescent and adult vaccine containing tetanus toxoid and reduced amounts of diphtheria toxoid and acellular pertussis vaccine

Introduction

Vaccines are one of the most important advances in modern medicine because of the dramatic impact they have had on infectious disease morbidity and mortality. Since the famous work of Edward Jenner in the late 1700s, global eradication of smallpox and significant declines in polio, diphtheria, tetanus, pertussis, measles, mumps, rubella, and *Haemophilus influenzae* type b (Hib) infections have occurred. However, despite widespread use of routine childhood vaccines in the Western hemisphere, continued surveillance is necessary to detect outbreaks of disease that can occur from international travel and lack or underuse of vaccination in certain patient populations.

Vaccines are a form of active immunity by which an antigen is administered that induces antibody formation and protection against infection. The immune response is produced when antigens stimulate T lymphocytes that subsequently direct B lymphocytes to produce immunoglobulin G, which provides long-lasting immune protection upon future exposure to the antigen. Some antigens such as bacterial cell wall polysaccharides produce a T cell–independent immune response by directly stimulating B lymphocytes, but the antibody produced is less functional and consists mainly of immunoglobulin M, which provides temporary immunity (Reference 1). Children younger than 2 years do not mount a sufficient response to these antigens because of their immature immune systems. Conjugating a cell wall polysaccharide to a protein molecule such as a nontoxic diphtheria toxin creates a T cell–dependent immune response that invokes a greater antibody response, irrespective of patient age, and provides a booster response when several vaccine doses are given over time.

The different classifications of vaccines vary in their immunity potential. Live vaccines contain attenuated organisms that undergo limited replication mimicking natural infection and can confer lifelong immunity with one or two doses. Development of immunity to live vaccines can be reduced or completely hindered by the presence of circulating antibody to the vaccine antigens. Administration of an antibody-containing blood product (e.g., immune globulin, packed red blood cells, fresh frozen plasma) within 2 weeks after a live injectable viral vaccine is given may interfere with viral replication; if this cannot be avoided, the vaccine dose should be repeated. Alternatively, if blood products are given first, it may be necessary to postpone vaccination with injectable live vaccines for up to 11 months after blood product administration. Similarly, administration of certain live viral vaccines can interfere with immunity to subsequently administered live vaccines. If two live injectable vaccines or live intranasal influenza vaccine are not administered simultaneously, they must be separated by at least 4 weeks to ensure an adequate immune response to the second live vaccine.

In contrast to live vaccines, inactivated vaccines consist of killed whole organisms or specific antigenic components that require several doses to induce long-lasting immunity. In most cases, booster doses are also needed to maintain immunity. These vaccines are not inactivated by circulating antibodies and can be administered any time before or after other inactivated or live vaccines. Inactivated vaccines can also differ in immunogenicity, which is dependent on their composition. Outer membrane polysaccharides are poorly immunogenic in infants, but when conjugated with carrier proteins, the immune response improves dramatically (Reference 2). Toxoids are inactive bacterial toxins usually combined with adjuvants such as aluminum to enhance antibody production against the toxin rather than the bacterial pathogen itself.

Routine Vaccines

Childhood immunization schedules are published annually in January by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). The currently recommended schedules for routine childhood and adolescent immunization are shown in Figure 1 and Figure 2 and can be found at www.cdc.gov/vaccines. Schedule updates and new information are published throughout the year in the *Morbidity and Mortality Weekly Report* (MMWR). Table 1 contains vaccine-specific information on administration schedules and requirements, adverse effects, precautions, and contraindications.

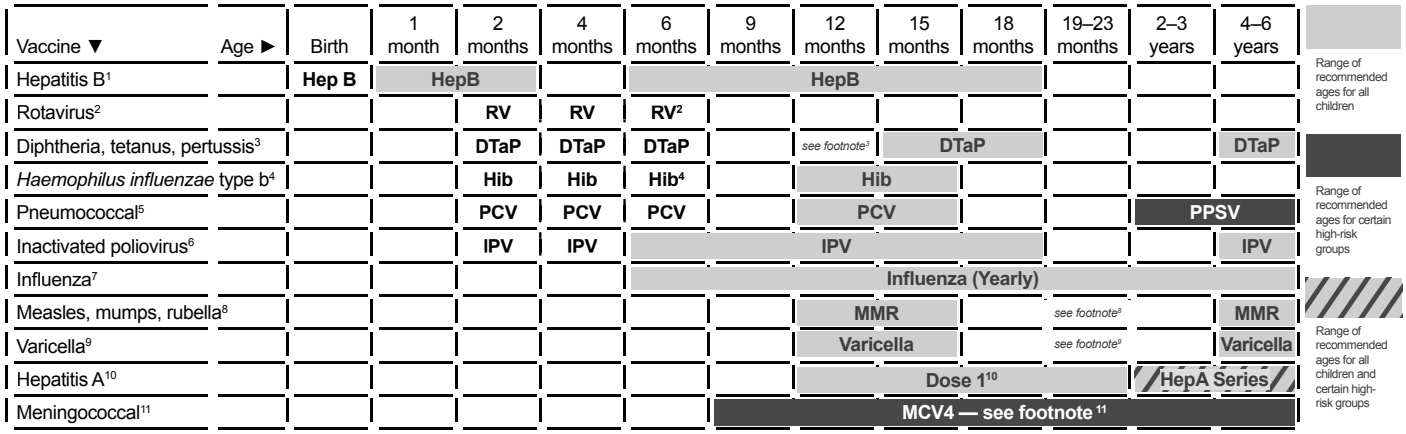
When there is an opportunity to vaccinate a child, health care providers must consult the recommended dosing schedule and determine whether any vaccines should be given at that health encounter. Recommended and minimum ages and intervals exist for all vaccines that are dosed in a series. Minimum ages are determined on the likelihood of inducing an immune response. Most inactivated vaccines do not induce an immune response before 6 weeks of age, except for hepatitis B vaccine. Live injectable vaccines such as measles, mumps, and rubella vaccine (MMR) and varicella may not induce immunity if given before 12 months of age because of the presence of maternal circulating antibodies. In general, increasing the interval between recommended doses does not reduce vaccine effectiveness, but decreasing the interval can reduce antibody response and interfere with immunity. Vaccine doses administered before the minimum recommended age or interval are not valid and must be repeated. Catch-up vaccine schedules incorporate the minimum ages and dosing intervals for vaccinations, and they can be used to update a child's immunization status that has fallen behind; these schedules are also available at www.cdc.gov/vaccines. Premature infants should be vaccinated at the same chronologic age as full-term infants and receive the full recommended doses (Reference 2).

Hepatitis B Vaccine

Hepatitis B virus is transmitted parenterally, perinatally, and sexually, potentially leading to acute or chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Children are most often infected during birth from infected mothers or from contact with infected household members and are at high risk of chronic infection and severe liver disease. Chronic infection is typically asymptomatic initially and may result in the spread of virus to others by those who are unaware of their chronic viremia. In the United States, acute infection occurs mainly during adulthood and can lead to chronic infection in up to 5% (References 1, 3). Because infants are at highest risk of acquiring asymptomatic chronic hepatitis B, vaccination efforts should focus on immunization after birth before hospital discharge. Catch-up vaccination will also help prevent hepatitis B infection and should target all infants, children, and adolescents not previously vaccinated as well as high-risk unvaccinated adults (Reference 3).

Hepatitis B vaccine is prepared through recombinant DNA technology in which hepatitis B surface antigen (HBsAg) is harvested and purified after production in yeast cells. It is available in two single-antigen (Engerix-B and Recombivax HB) and three combination vaccines (Twinrix, Comvax, and Pediarix; refer to Combination Vaccines section and Table 2) containing 10–40 mcg of HBsAg protein per milliliter.

The recommended administration schedule varies with patient age. Routine infant immunization should begin within 12 hours of birth with single-antigen vaccine to prevent perinatal infection, followed by the second and third doses given at 1–2 months and 6–18 months of age. If a combination vaccine containing hepatitis B antigen is used to complete the series after the birth dose, additional doses are given at 2, 4, and 6 months of age. Preterm infants weighing less than 2 kg do not mount a sufficient immune response to the birth dose; this dose can be delayed until the child is 1 month of age if born to an HBsAg-negative mother. If a birth dose must be given to a preterm infant weighing less than 2 kg, the dose should not be counted, and the child should receive three additional doses beginning at 1 month of age (Reference 3). Unvaccinated adolescents should receive a three-dose series of single-antigen vaccine (two doses separated by 4 weeks, with the third dose 4–6 months after the second dose); an alternative two-dose series with Recombivax HB is approved for adolescents 11–15 years of age, but no data exist on its long-term protection.



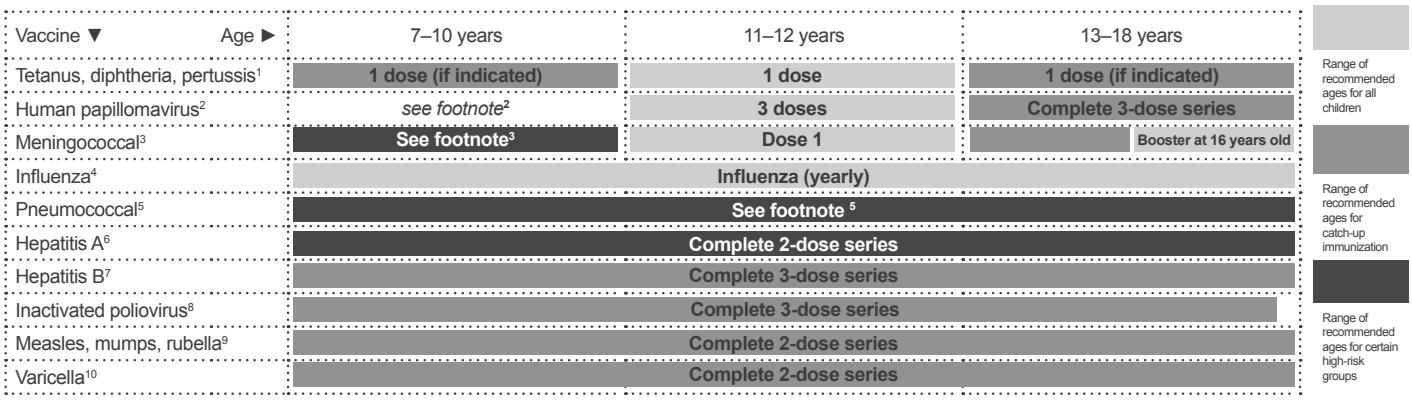
This schedule includes recommendations in effect as of December 23, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).

1. **Hepatitis B (HepB) vaccine.** (Minimum age: birth)
   At birth:
   - Administer monovalent HepB vaccine to all newborns before hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)–positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).
   - If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine for infants weighing ≥2,000 grams, and HepB vaccine plus HBIG for infants weighing <2,000 grams. Determine mother's HBsAg status as soon as possible and, if she is HBsAg-positive, administer HBIG for infants weighing ≥2,000 grams (no later than age 1 week).

   Doses after the birth dose:
   - The second dose should be administered at age 1 to 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Administration of a total of 4 doses of HepB vaccine is permissible when a combination vaccine containing HepB is administered after the birth dose.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine starting as soon as feasible (Figure 3).
   - The minimum interval between dose 1 and dose 2 is 4 weeks, and between dose 2 and 3 is 8 weeks. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose.
2. **Rotavirus (RV) vaccines.** (Minimum age: 6 weeks for both RV-1 [Rotarix] and RV-5 [Rota Teq])
   - The maximum age for the first dose in the series is 14 weeks, 6 days; and 8 months, 0 days for the final dose in the series. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
   - If RV-1 (Rotarix) is administered at ages 2 and 4 months, a dose at 6 months is not indicated.
3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.** (Minimum age: 6 weeks)
   - The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.
4. ***Haemophilus influenzae* type b (Hib) conjugate vaccine.** (Minimum age: 6 weeks)
   - If PRP-OMP (PedvaxHIB or Comvax [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.
   - Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years.
5. **Pneumococcal vaccines.** (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])
   - Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
   - For children who have received an age-appropriate series of 7-valent PCV (PCV7), a single supplemental dose of 13-valent PCV (PCV13) is recommended for:
     — All children aged 14 through 59 months
     — Children aged 60 through 71 months with underlying medical conditions.
   - Administer PPSV at least 8 weeks after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. See *MMWR* 2010:59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.
6. **Inactivated poliovirus vaccine (IPV).** (Minimum age: 6 weeks)
   - If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years.
   - The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.
7. **Influenza vaccines.** (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])
   - For most healthy children aged 2 years and older, either LAIV or TIV may be used. However, LAIV should not be administered to some children, including 1) children with asthma, 2) children 2 through 4 years who had wheezing in the past 12 months, or 3) children who have any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV, see *MMWR* 2010;59(No. RR-8), available at http://www.cdc.gov/mmwr/pdf/rr/rr5908.pdf.
   - For children aged 6 months through 8 years:
     — For the 2011–12 season, administer 2 doses (separated by at least 4 weeks) to those who did not receive at least 1 dose of the 2010–11 vaccine. Those who received at least 1 dose of the 2010–11 vaccine require 1 dose for the 2011–12 season.
     — For the 2012–13 season, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations.
8. **Measles, mumps, and rubella (MMR) vaccine.** (Minimum age: 12 months)
   - The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
   - Administer MMR vaccine to infants aged 6 through 11 months who are traveling internationally. These children should be revaccinated with 2 doses of MMR vaccine, the first at ages 12 through 15 months and at least 4 weeks after the previous dose, and the second at ages 4 through 6 years.
9. **Varicella (VAR) vaccine.** (Minimum age: 12 months)
   - The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose.
   - For children aged 12 months through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
10. **Hepatitis A (HepA) vaccine.** (Minimum age: 12 months)
    - Administer the second (final) dose 6 to18 months after the first.
    - Unvaccinated children 24 months and older at high risk should be vaccinated. See *MMWR* 2006;55(No. RR-7), available at http://www.cdc.gov/mmwr/pdf/rr/rr5507.pdf.
    - A 2-dose HepA vaccine series is recommended for anyone aged 24 months and older, previously unvaccinated, for whom immunity against hepatitis A virus infection is desired.
11. **Meningococcal conjugate vaccines, quadrivalent (MCV4).** (Minimum age: 9 months for Menactra [MCV4-D], 2 years for Menveo [MCV4-CRM])
    - For children aged 9 through 23 months 1) with persistent complement component deficiency; 2) who are residents of or travelers to countries with hyperendemic or epidemic disease; or 3) who are present during outbreaks caused by a vaccine serogroup, administer 2 primary doses of MCV4-D, ideally at ages 9 months and 12 months or at least 8 weeks apart.
    - For children aged 24 months and older with 1) persistent complement component deficiency who have not been previously vaccinated; or 2) anatomic/functional asplenia, administer 2 primary doses of either MCV4 at least 8 weeks apart.
    - For children with anatomic/functional asplenia, if MCV4-D (Menactra) is used, administer at a minimum age of 2 years and at least 4 weeks after completion of all PCV doses.
    - See *MMWR* 2011;60:72–6, available at http://www.cdc.gov/mmwr/pdf/wk/mm6003. pdf, and Vaccines for Children Program resolution No. 6/11-1, available at http://www. cdc.gov/vaccines/programs/vfc/downloads/resolutions/06-11mening-mcv.pdf, and *MMWR* 2011;60:1391–2, available at http://www.cdc.gov/mmwr/pdf/wk/mm6040. pdf, for further guidance, including revaccination guidelines.

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/recs/acip), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).
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Figure 1. Recommended immunization schedule for persons aged 0 through 6 years—United States, 2012 (for those who fall behind or start late, see the catch-up schedule).



This schedule includes recommendations in effect as of December 23, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).

1. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine.** (Minimum age: 10 years for Boostrix and 11 years for Adacel)
   - Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
   - Tdap vaccine should be substituted for a single dose of Td in the catch-up series for children aged 7 through 10 years. Refer to the catch-up schedule if additional doses of tetanus and diphtheria toxoid–containing vaccine are needed.
   - Tdap vaccine can be administered regardless of the interval since the last tetanus and diphtheria toxoid–containing vaccine.
2. **Human papillomavirus (HPV) vaccines (HPV4 [Gardasil] and HPV2 [Cervarix]).** (Minimum age: 9 years)
   - Either HPV4 or HPV2 is recommended in a 3-dose series for females aged 11 or 12 years. HPV4 is recommended in a 3-dose series for males aged 11 or 12 years.
   - The vaccine series can be started beginning at age 9 years.
   - Administer the second dose 1 to 2 months after the first dose and the third dose 6 months after the first dose (at least 24 weeks after the first dose).
   - See *MMWR* 2010;59:626–32, available at http://www.cdc.gov/mmwr/pdf/wk/mm5920.pdf.
3. **Meningococcal conjugate vaccines, quadrivalent (MCV4).**
   - Administer MCV4 at age 11 through 12 years with a booster dose at age 16 years.
   - Administer MCV4 at age 13 through 18 years if patient is not previously vaccinated.
   - If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks after the preceding dose.
   - If the first dose is administered at age 16 years or older, a booster dose is not needed.
   - Administer 2 primary doses at least 8 weeks apart to previously unvaccinated persons with persistent complement component deficiency or anatomic/functional asplenia, and 1 dose every 5 years thereafter.
   - Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of MCV4, at least 8 weeks apart.
   - See *MMWR* 2011;60:72–76, available at http://www.cdc.gov/mmwr/pdf/wk/mm6003.pdf, and Vaccines for Children Program resolution No. 6/11-1, available at http://www.cdc.gov/vaccines/programs/vfc/downloads/resolutions/06-11mening-mcv.pdf, for further guidelines.
4. **Influenza vaccines (trivalent inactivated influenza vaccine [TIV] and live, attenuated influenza vaccine [LAIV]).**
   - For most healthy, nonpregnant persons, either LAIV or TIV may be used, except LAIV should not be used for some persons, including those with asthma or any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV, see *MMWR* 2010;59(No.RR-8), available at http://www.cdc.gov/mmwr/pdf/rr/rr5908.pdf.
   - Administer 1 dose to persons aged 9 years and older.
   - For children aged 6 months through 8 years:
     — For the 2011–12 season, administer 2 doses (separated by at least 4 weeks) to those who did not receive at least 1 dose of the 2010–11 vaccine. Those who received at least 1 dose of the 2010–11 vaccine require 1 dose for the 2011–12 season.
     — For the 2012–13 season, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations.
5. **Pneumococcal vaccines (pneumococcal conjugate vaccine [PCV] and pneumococcal polysaccharide vaccine [PPSV]).**
   - A single dose of PCV may be administered to children aged 6 through 18 years who have anatomic/functional asplenia, HIV infection or other immunocompromising condition, cochlear implant, or cerebral spinal fluid leak. See *MMWR* 2010:59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.
   - Administer PPSV at least 8 weeks after the last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. A single revaccination should be administered after 5 years to children with anatomic/functional asplenia or an immunocompromising condition.
6. **Hepatitis A (HepA) vaccine.**
   - HepA vaccine is recommended for children older than 23 months who live in areas where vaccination programs target older children, who are at increased risk for infection, or for whom immunity against hepatitis A virus infection is desired. See *MMWR* 2006;55(No. RR-7), available at http://www.cdc.gov/mmwr/pdf/rr/rr5507.pdf.
   - Administer 2 doses at least 6 months apart to unvaccinated persons.
7. **Hepatitis B (HepB) vaccine.**
   - Administer the 3-dose series to those not previously vaccinated.
   - For those with incomplete vaccination, follow the catch-up recommendations (Figure 3).
   - A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
8. **Inactivated poliovirus vaccine (IPV).**
   - The final dose in the series should be administered at least 6 months after the previous dose.
   - If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age.
   - IPV is not routinely recommended for U.S. residents aged18 years or older.
9. **Measles, mumps, and rubella (MMR) vaccine.**
   - The minimum interval between the 2 doses of MMR vaccine is 4 weeks.
10. **Varicella (VAR) vaccine.**
    - For persons without evidence of immunity (see *MMWR* 2007;56[No. RR-4], available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf), administer 2 doses if not previously vaccinated or the second dose if only 1 dose has been administered.
    - For persons aged 7 through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.
    - For persons aged 13 years and older, the minimum interval between doses is 4 weeks.

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/recs/acip), the American Academy of Pediatrics (http://www.aap.org), and the American Academy of Family Physicians (http://www.aafp.org).
Department of Health and Human Services • Centers for Disease Control and Prevention

Figure 2. Recommended immunization schedule for persons aged 7 through 18 years—United States, 2012 (for those who fall behind or start late, see the schedule below and the catch-up schedule).

Table 1. Vaccine-Specific Administration Information, Adverse Effects, Precautions, and Contraindications

Vaccine	Recommended Administration Schedule	Route of Administration	Vaccine-Specific Adverse Effects	Vaccine-Specific Precautions	Vaccine-Specific Contraindications
Diphtheria, tetanus, acellular pertussis (DTaP or Tdap) Diphtheria and tetanus toxoids (Td or DT)	DTaP: 2 months, 4 months, 6 months, 15–18 months, and 4–6 years Tdap: single dose between 11–18 years (11–12 years is preferred) Td: booster dose every 10 years following adolescent Tdap dose DT: not routinely recommended	IM	Exaggerated local (Arthus) reaction with limb swelling Pertussis-containing vaccines only: moderate/severe systemic effects (temperature ≥ 105°F, febrile seizures, persistent crying ≥ 3 hours, hypotonic or hyporesponsive episode) Tdap only: syncope in adolescents	GBS within 6 weeks of prior tetanus-containing vaccine Arthus reaction after prior tetanus-containing vaccine; defer vaccine until ≥ 10 years have elapsed since last tetanus-containing vaccine DTaP only: temperature ≥ 105°F or collapse/shock-like state or persistent, inconsolable crying for ≥ 3 hours within 48 hours of prior vaccine dose; seizures within 3 days of prior vaccine dose Pertussis-containing vaccines: progressive or unstable neurologic disorder, uncontrolled seizures, or progressive encephalopathy; defer until condition stabilizes	Pertussis-containing vaccines only: encephalopathy within 7 days of prior vaccine dose with no other cause
Haemophilus influenzae type b (Hib)	2 months, 4 months, 6 months, and 12–15 months (6 month dose not needed if PedvaxHIB was given at 2 months and 4 months)	IM			Age younger than 6 weeks
Hepatitis A	Two dose series: first dose at 12–23 months; second dose 6–18 months after first dose	IM		Pregnancy	
Hepatitis B	Birth, 1–2 months, and 6–18 months	IM		Newborns weighing less than 2 kg if mother is hepatitis B surface antigen negative	
Human papillomavirus (HPV)	Three dose series: First dose at 11–12 years; second dose 1–2 months after first dose; third dose 6 months after first dose	IM	Syncope in adolescents	Pregnancy	
Live attenuated influenza (LAIV)	Annually beginning at 2 years Children between 2 and 8 years of age not vaccinated in previous years require 2 doses separated by at least 4 weeks	Intranasal	Wheezing (between 6 and 23 months of age) Rhinorrhea or nasal congestion	GBS within 6 weeks of prior influenza vaccine Receipt of antivirals (oseltamivir, zanamivir, amantadine, rimantadine) 48 hours before vaccination; avoid these for 14 days after vaccination	Age <2 years or ≥50 years Possible reactive airway disease in children 2–4 years of age (history of wheezing) Pregnancy Immunosuppression Certain chronic medical conditions Chronic use of aspirin Severe egg allergy
Inactivated influenza (TIV)	Annually beginning at 6 months Children between 6 months and 8 years of age not vaccinated in previous years require 2 doses separated by at least 4 weeks	IM	GBS	GBS within 6 weeks of prior influenza vaccine	Severe egg allergy other than hives

Vaccine	Recommended Administration Schedule	Route of Administration	Vaccine-Specific Adverse Effects	Vaccine-Specific Precautions	Vaccine-Specific Contraindications
Measles, mumps, rubella (MMR) Measles, mumps, rubella, varicella (MMRV)	12–15 months and 4–6 years	SC	Transient rash 7–10 days postvaccination Thrombocytopenia Transient lymphadenopathy or parotitis MMRV: febrile seizures MMRV: varicella-like rash within 14 days of vaccine	Receipt of antibody-containing blood product (within up to 11 months); defer for appropriate interval depending on product received (Reference 2) History of thrombocytopenia or thrombocytopenic purpura Need for tuberculin skin testing MMRV only: personal or family history of febrile seizures; administer MMR and varicella vaccines separately MMRV only: chronic aspirin use; avoid salicylates for 6 weeks after receipt of MMRV vaccine (per manufacturer)	Pregnancy Severe immunodeficiency or immunosuppression Severe allergic reaction to neomycin or gelatin
Meningococcal conjugate (MCV)	11–12 years; booster dose at 16 years	IM	Syncope in adolescents GBS	History of GBS	
Pneumococcal conjugate (PCV13)	2 months, 4 months, 6 months, and 12–15 months	IM			
Pneumococcal polysaccharide (PPSV)	Not routinely recommended; use in high–risk groups only	IM			Children younger than 2 years
Poliovirus, inactivated (IPV)	2 months, 4 months, 6–18 months, and 4–6 years	IM or SC			Severe allergic reaction to neomycin, streptomycin, or polymyxin B
Rotavirus (RV)	2 months, 4 months, and 6 months (6 month dose not needed if Rotarix was given at 2 months and 4 months)	Oral		Immunosuppression other than SCID Acute, moderate, or severe gastroenteritis Chronic gastrointestinal disease Spina bifida (Rotarix only) Hospitalized infants	Severe allergy to latex (Rotarix only) History of intussusception SCID Children younger than 6 weeks
Varicella (VAR)	12–15 months and 4–6 years	SC	Varicella-like rash within 14 days of vaccine	Receipt of antibody-containing blood product (within up to 11 months); defer for appropriate interval depending on product received (Reference 2) Receipt of antivirals (acyclovir, famciclovir, valacyclovir) 24 hours before vaccination; avoid these for 14 days after vaccination Chronic aspirin use; avoid salicylates for 6 weeks after receipt of varicella vaccine (per manufacturer)	Pregnancy Severe immunodeficiency or immunosuppression Severe allergic reaction to neomycin or gelatin

GBS = Guillain-Barré syndrome; IM = intramuscular; SC = subcutaneous; SCID = severe combined immunodeficiency.

Diphtheria and Tetanus Toxoids and Pertussis Vaccine

Diphtheria is a toxin-mediated disease that destroys nasopharyngeal tissue and forms membranes covering the pharynx, uvula, tonsils, and soft palate, which can lead to respiratory obstruction. Diphtheria can also involve the skin, conjunctiva, and vulvovaginal area. *Corynebacterium diphtheriae* produces its toxin only when it is infected by a bacteriophage carrying the tox gene. Systemic toxemia caused by toxin absorption can cause myocarditis, peripheral neuritis, and thrombocytopenia. Diphtheria transmission occurs most frequently by person-to-person spread from the respiratory tract. Although diphtheria disease is rare in the United States with only five cases reported since 2000, *C. diphtheriae* continues to circulate in previously endemic areas, particularly Native American communities (Reference 1).

Diphtheria toxoid is an inactivated *C. diphtheriae* toxin adsorbed to aluminum to enhance its immunogenicity. It is only available in combination with either tetanus toxoid or both tetanus toxoid and pertussis vaccine. There are two diphtheria toxoid strengths; the pediatric strength (designated by capital *D*) contains 3–4 times the amount of the adult strength (designated by lowercase *d*). Routine childhood vaccination begins as early as 6 weeks of age and consists of a five-dose series given in combination with tetanus toxoid and acellular pertussis vaccine (as DTaP; see Table 1). Booster doses in combination with tetanus toxoid (Td) are given every 10 years after completion of the childhood series and adolescent Tdap booster because of waning immunity during adulthood.

Tetanus is a toxin-mediated disease acquired from the environment, mainly soil, and is the only vaccine-preventable disease that is not contagious. *Clostridium tetani* spores enter the body, usually through a wound, and germinate in anaerobic conditions, causing the production of two toxins that act in the central nervous system. One toxin, tetanospasmin, blocks neurotransmitter inhibitor impulses, causing severe muscle contractions and spasms. The most common form of tetanus is generalized; it begins with lockjaw and descends downward to affect the neck, esophagus, and abdomen. Additional manifestations include tachycardia, elevated blood pressure, fever, and sweating. Tetanus is rare in the United States, with up to 100 cases reported annually, but it is common in developing countries and often afflicts neonates whose mothers were not immune (References 1, 4).

Tetanus toxoid is a formalin-inactivated toxin that is available as an adsorbed (onto aluminum hydroxide) or non-adsorbed toxoid. The adsorbed toxoid is preferred because it elicits a stronger and longer-lasting immune response (Reference 1). It is available as a single-antigen product, but it is preferable to administer as a combination product with either diphtheria toxoid (as DT or Td) or diphtheria toxoid and acellular pertussis vaccine (as DTaP or Tdap) to provide continued protection against multiple infections with one vaccine dose. The primary childhood series should be given with DTaP (Table 1). Because immunity wanes with time, booster doses should be given as Td every 10 years after the primary series and adolescent Tdap booster. Patients who present with minor or uncontaminated wounds should receive a tetanus booster if it has been 10 years or more since their last tetanus-containing vaccine. Patients with moderate to severe wounds or contaminated wounds should be vaccinated if they have not received a tetanus-containing vaccine in the preceding 5 years. Individuals who experienced an Arthus reaction characterized by severe pain, swelling, and induration within 4–12 hours after a tetanus vaccine should not receive a tetanus-containing vaccine any earlier than 10 years after the last tetanus dose, even for wound management.

Table 2. Combination Vaccines and Indications

Vaccine Brand Name	Vaccine Components	Indications
Comvax	Hepatitis B, Hib	For doses at 2, 4, and 12–15 months of age
Kinrix	DTaP, IPV	For fifth DTaP dose and fourth IPV dose at 4–6 years of age
Menhibrix	N. meningitidis serogroups C and Y, Hib	For doses at 2, 4, 6, and 12–15 months of age
Pediarix	DTaP, hepatitis B, IPV	For doses at 2, 4, and 6 months of age; not for boosters
Pentacel	DTaP, IPV, Hib	For doses at 2, 4, 6, and 15–18 months of age
ProQuad	MMR, varicella	For 1–12 years of age; consider for only second dose in series
Twinrix	Hepatitis A, hepatitis B	18 years and older; three-dose series

DTaP = pediatric vaccine containing diphtheria and tetanus toxoids and acellular pertussis vaccine; Hib = Haemophilus influenzae type b; IPV = polio virus, inactivated; MMR = measles, mumps, rubella.

Pertussis, or whooping cough, is a highly contagious respiratory tract infection caused by *Bordetella pertussis*. It is spread through respiratory droplets that are inhaled or through direct contact with contaminated secretions that reach the mucus membranes. Toxins released by *B. pertussis* paralyze the cilia on respiratory epithelial cells and promote inflammation within the respiratory tract, which interferes with the clearance of secretions. Classic pertussis occurs in three stages: catarrhal, paroxysmal, and convalescence. The catarrhal stage is characterized by rhinorrhea, sneezing, low-grade fever, and mild cough, lasting 1–2 weeks. The cough progressively worsens until paroxysms of coughing become interrupted with the characteristic "whoop" sound upon inspiration. In this paroxysmal stage, cyanosis and posttussive vomiting and exhaustion are common, lasting for 1–6 weeks. Gradual improvement occurs in the convalescent stage over a few weeks to months. Adolescents and adults typically have a milder and shorter course of illness than do infants and young children.

The incidence of pertussis in the United States has increased since the early 1980s, when around 3000 cases were reported annually (Reference 1). More than 27,000 cases were reported in 2010, the largest number since 1959. Although the highest annual incidence occurs in infants younger than 6 months, 60% of cases are now reported in people 11 years and older (Reference 5). Increased recognition of disease and waning immunity are possible causes for the large number of cases reported in this age group. Mortality, which remains highest in infants younger than 3 months, is usually caused by secondary bacterial pneumonia (Reference 1).

Pertussis vaccines available in the United States are acellular, containing purified subunits of *B. pertussis* such as pertussis toxin, filamentous hemagglutinin, and pertactin. Acellular vaccines are less reactogenic than their predecessor whole-cell pertussis vaccines, which caused more local reactions, fevers, and systemic effects. Whole-cell vaccines are no longer available in the United States but are still used in many countries. Three pediatric acellular vaccines are available (all in combination with diphtheria and tetanus toxoids, as DTaP) that contain different types and amounts of pertussis antigens: Daptacel, Infanrix, and Tripedia. The primary childhood series consists of five doses given at 2, 4, 6, 15–18 months, and 4–6 years (as DTaP). The series should be completed with the same brand of DTaP when possible, but any available brand can be used for continuation or completion of the series. The DTaP vaccines are also available in combination with other vaccines (Pediarix, Kinrix, and Pentacel; refer to Combination Vaccines section and Table 2), each having different administration schedules.

Two adolescent and adult acellular pertussis vaccines in combination with diphtheria and tetanus toxoids (Tdap, as Boostrix and Adacel) are available for use as single booster doses to combat waning pertussis immunity after childhood and subsequent spread to infants. These combination vaccines contain reduced amounts of pertussis antigens (designated by lowercase *p*) compared with the pediatric formulations (designated by capital *P*), but they have an amount of diphtheria and tetanus toxoids identical to the Td booster vaccines. A single Tdap dose is recommended for all children 11–18 years of age regardless of DTaP series completion and for children 7–10 years of age who are not fully vaccinated against pertussis (Reference 6). In addition, Tdap should be given in place of Td for wound management if the patient has not previously received a dose of Tdap. Other patients who should receive a single Tdap dose if they have not had one previously are health care personnel and those in close contact with infants (i.e., those younger than 12 months), including child care providers and new parents (including postpartum women) and grandparents (References 7, 8). There is no minimum interval recommended between receipt of Tdap and the last tetanus- or diphtheria-containing vaccine. After Tdap is received, all subsequent booster doses should be with Td.

Hib Vaccine

H. influenzae is a common bacterial organism that colonizes the respiratory tract and causes minor infections, such as otitis media and sinusitis, or invasive disease such as meningitis, epiglottitis, pneumonia, and sepsis. Transmission is primarily through respiratory droplet spread. *H. influenzae* can be encapsulated with a polysaccharide capsule that contributes to its virulence, or it can be nonencapsulated. *H. influenzae* type b is an encapsulated strain that causes invasive infections in children younger than 5 years and was historically the most common cause of bacterial meningitis. The incidence of invasive Hib disease in the United States has declined by more than 99% since the Hib vaccine was introduced in the late 1980s. Since 1996, less than 100 cases of invasive Hib disease are reported annually in children younger than 5 years (Reference 1).

The Hib vaccines are conjugated vaccines in which polysaccharide capsular components are chemically linked to protein carriers that elicit a T cell–independent immune response that elicits protection in young children. Earlier Hib vaccines consisted of unconjugated polysaccharides that were poorly immunogenic, particularly in children younger than 2 years. Three conjugated vaccines are available: two of them use tetanus toxoid as the protein carrier (ActHIB and Hiberix), and one uses *Neisseria meningitidis* group B outer membrane protein (PedvaxHIB). In addition, three combination

vaccines contain conjugated Hib vaccine (Comvax, Menhibrix, and Pentacel; refer to Combination Vaccines section and Table 2). The primary childhood series is given at 2, 4, and 6 months (with ActHIB) or at 2 and 4 months (with PedvaxHIB), followed by a booster dose at 12–15 months (with ActHIB, Hiberix, or PedvaxHIB). No Hib-containing vaccine should be given to infants younger than 6 weeks because the immune response to subsequent doses is reduced (Reference 1). PedvaxHIB and ActHIB are considered interchangeable and can be given for any of the primary or booster doses; however, if PedvaxHIB is not given at 2 and 4 months, a 6-month dose of either vaccine must be given. Hiberix is only approved for use as the booster dose.

Although Hib vaccines are only recommended for routine use in children younger than 5 years, certain patient populations may be at increased risk of Hib infection. One dose of any Hib vaccine may be beneficial for patients who were not previously vaccinated in childhood and have sickle cell disease or asplenia, human immunodeficiency virus (HIV) infection, certain immunodeficiencies, immunosuppression from cancer chemotherapy, or who received a hematopoietic stem cell transplant (References 1, 2).

Pneumococcal Vaccines

Streptococcus pneumoniae is a common cause of otitis media, sinusitis, pneumonia, bacteremia, and meningitis that is associated with significant morbidity and mortality in children younger than 2 years. Transmission occurs primarily through respiratory droplet spread from person-to-person and through autoinoculation in individuals who carry the organism in their upper respiratory tract. Ninety capsular polysaccharide serotypes have been identified, and the 10 most common serotypes cause more than 60% of invasive disease globally (Reference 1). Pneumococcal antibiotic resistance has escalated in recent years, and protection against invasive pneumococcal infection through vaccination is vital. Since the introduction of the first conjugated 7-valent pediatric vaccine (PCV7) in 2000, there has been a 99% reduction in invasive disease in children younger than 5 years caused by the seven vaccine serotypes and an additional serotype, 6A, for which the vaccine provided cross-protection (Reference 1). Replacement with non-vaccine serotypes (e.g., 19A) has emerged, contributing to increased rates of invasive disease caused by these serotypes and the subsequent introduction of expanded multivalent vaccines (References 9, 10).

Two pneumococcal vaccines are currently available in the United States: a 13-valent pneumococcal conjugate vaccine (PCV13) and a 23-valent pneumococcal polysaccharide vaccine (PPSV23). The vaccines target different patient populations and age groups, and they are not interchangeable. Although all children younger than 5 years are at increased risk of invasive pneumococcal disease, some factors increase the risk even further. Asplenia, HIV infection, certain racial groups (Alaska natives, African Americans, American Indians), day care attendance, and cochlear implants are independent risk factors for invasive pneumococcal disease.

The PCV13 is a conjugated polysaccharide vaccine that elicits immunity in young children through a T cell–independent antibody response. It contains purified capsular polysaccharide of 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) conjugated to a nontoxic diphtheria toxin. Available beginning in 2010 as a replacement for PCV7, it is administered at 2, 4, and 6 months of age with a booster dose at 12–15 months of age. An additional dose of PCV13 is recommended for children between 14 and 59 months of age who completed their primary pneumococcal vaccine series with PCV7 (Reference 11). Routine use of PCV13 is not recommended for healthy children 5 years and older, but children with certain chronic medical conditions should receive an additional PCV13 dose (administered at least 8 weeks after the most recent pneumococcal vaccine dose) between 14 and 71 months of age. It may also be considered for those up to 18 years old with certain medical conditions who have not received PCV13 previously. These conditions include chronic heart and lung disease, diabetes, sickle cell disease, cochlear implants, HIV infection, and other immunocompromising states.

The PPSV23 vaccine contains capsular polysaccharides from the 23 pneumococcal serotypes that are most prevalent and most associated with antibiotic resistance. Young children do not mount a sufficient immune response to this vaccine, so it cannot be given to children younger than 2 years. A single dose of PPSV23 (administered at least 8 weeks after the most recent pneumococcal vaccine dose) is recommended for children 2 years and older with the following high-risk conditions: chronic cardiovascular or pulmonary disease, diabetes, asplenia or sickle cell disease, cochlear implants, chronic renal failure, or immunocompromising conditions. This dose is in addition to the PCV13 vaccine series recommended above. Antibody response to PPSV23 declines within 10 years of vaccination and can occur within 3–5 years in children. Revaccination with a single dose is recommended for children who remain at highest risk of invasive disease caused by asplenia, immunosuppression, or chronic renal failure; this revaccination consists of one dose given 3–5 years after the first PPSV23 dose (Reference 1).

Poliovirus Vaccine

Poliomyelitis is a highly contagious viral infection that, although usually asymptomatic, can result in a rapid deterioration to flaccid paralysis that may be permanent. Poliovirus is spread through the fecal-oral route and can be excreted in stool for several weeks after infection, allowing easy spread to household contacts. After the first inactivated poliovirus vaccine (IPV) was introduced in 1955 and after the subsequent introduction of live oral poliovirus vaccine (OPV) in 1961, the incidence of paralytic polio in the United States dropped dramatically from up to 20,000 cases annually to less than 100 in 1965 (Reference 1). The last endemic case of paralytic polio in the United States was reported in 1979, but vaccine-associated paralytic polio continued to occur because of OPV use. In 2000, ACIP recommended eliminating the use of OPV in the United States, but it is necessary to use in areas of the world where poliovirus continues to circulate.

The inactivated poliovirus vaccine, which is the only available polio vaccine in the United States, contains three serotypes that are inactivated by formaldehyde. It elicits a strong immune response but produces less gastrointestinal immunity than OPV and has an unknown duration of protection. The childhood series should be given at 2, 4, and 6–18 months of age with a booster dose at 4–6 years of age. This vaccine is commonly administered in combination with other antigens (as Pediarix, Kinrix, or Pentacel; refer to Combination Vaccines section and Table 2), but it is also available as a single vaccine.

Rotavirus Vaccine

Rotavirus is a highly contagious virus spread through the fecal-oral route and is the most common cause of gastroenteritis in children worldwide. In the pre-vaccine era, most children were infected in the first 5 years of life. Clinical manifestations of rotavirus infection vary from asymptomatic to mild, watery diarrhea to severe dehydration from vomiting and diarrhea. Severe dehydration from rotavirus infection occurs mainly among children younger than 2 years and is associated with significant mortality in developing countries. Globally, more than 0.5 million deaths occur annually from rotavirus infection and dehydration, but in the United States, only 20–60 deaths occurred annually before routine rotavirus vaccination (References 1, 12). Direct and indirect costs of rotavirus infection were about $1 billion annually in the United States because of emergency department and physician office visits and subsequent hospitalizations (Reference 1). The first rotavirus vaccine was a tetravalent rhesus-based vaccine introduced in 1998, but it was associated with a markedly increased risk of intussusception and was withdrawn in 1999. In 2006, a rotavirus vaccine was reintroduced that has led to a more than 67% reduction in rotavirus activity and a delay in its seasonal spike pattern by 2–4 months (Reference 12).

Two live oral rotavirus vaccines are available in the United States: RotaTeq and Rotarix. RotaTeq, which contains five live human-bovine reassortant rotavirus strains, became available in 2006. Rotarix, which contains one live attenuated human rotavirus strain, became available in 2008. These vaccines do not completely prevent rotavirus infection, but studies have shown an 85% to 98% reduction in severe gastroenteritis and an 85% to 100% reduction in hospitalizations after vaccination (Reference 1). ACIP does not prefer one rotavirus vaccine over the other because they have similar efficacy and safety data. The administration schedule varies with each vaccine: RotaTeq is given as a three-dose series and Rotarix as a two-dose series, both beginning at 2 months of age with subsequent doses given 1–2 months apart. The maximum age for any rotavirus vaccine dose is 8 months 0 days because the previously reported high risk of intussusception was associated with increasing age at the time of vaccination. Although the vaccines are not considered interchangeable, the vaccine series can be continued or completed with either product. If any dose of RotaTeq is administered in the schedule, a three-dose series must be given. Rotavirus vaccine should not be administered to immunocompromised individuals (and is contraindicated in severe combined immunodeficiency) because it is a live viral vaccine and could cause rotavirus infection in these patients. Rotavirus vaccine can be given to infants living with immunocompromised individuals, and it can be given to infants regardless of antibody or blood product administration.

Influenza Vaccine

Influenza is a highly contagious viral respiratory infection that causes significant morbidity and mortality among young children and the elderly. It is spread through respiratory droplets that are inhaled or through direct contact with contaminated secretions that reach the mucus membranes. Infection usually occurs during the winter months in the Northern Hemisphere, and although all age groups are affected, children have the highest infection rate. Classic symptoms of influenza in adults include rapid onset of fever, sore throat, myalgia, headache, nonproductive cough, malaise, and rhinitis, whereas children often also experience nausea, vomiting, and otitis media (see Lower Respiratory Tract Infections chapter). Pneumonia is a severe complication that results from primary influenza infection or secondary bacterial infection. Severe illness, hospitalization, and death are most likely to occur in the elderly, children younger than 2 years, and those with underlying conditions, including cardiopulmonary disease and pregnancy.

Recent data estimate that an average of 24,000 deaths occur annually in all age groups from influenza in the United States (Reference 13). The best method of protection against influenza is through vaccination.

Human influenza disease is caused by influenza A and B viruses that circulate concurrently. Influenza A typically causes moderate to severe infection and affects all age groups. It is further subtyped by its surface antigens, hemagglutinin (H) and neuraminidase (N). Human infections typically occur with subtypes categorized as H1–H3 and N1 and N2, but strains that usually infect animals (e.g., H5N1) rarely infect humans. Influenza B usually causes milder infection and infects children more often. It is not subtyped but is categorized as one of two lineages (Yamagata and Victoria) that have been circulating for many years. New influenza virus variants are created by antigenic point mutations that evade host immunity and perpetuate the infectious cycle, known as antigenic drift. This occurs mainly with influenza A and is responsible for seasonal influenza epidemics and the recommendation for annual vaccination with vaccine composed of strains predicted to be circulating during the upcoming influenza season. Antigenic shift occurs when influenza A virus acquires a new hemagglutinin or neuraminidase surface antigen as a result of genetic reassortment; these strains have pandemic potential because they are dissimilar to previously circulating influenza strains.

Two types of influenza vaccine are currently available for prevention of seasonal influenza in children, both of which contain the same viral strains or subunit antigens of two influenza A subtypes and one influenza B strain. One is a trivalent inactivated injectable influenza vaccine (TIV), and one is a trivalent live attenuated influenza vaccine (LAIV) that is cold adapted, allowing virus replication to occur locally in the nasopharynx after intranasal administration. The LAIV strains do not replicate well in warm environments such as the lung. Studies report that LAIV is 32%–58% more protective against culture-confirmed influenza infections than TIV in children 6 months to 17 years of age with no significant differences noted in adults (Reference 14). A trivalent inactivated intradermal vaccine was recently approved for use by the U.S. Food and Drug Administration (FDA) in adults 18–64 years of age, and it is currently being studied in children. Beginning with the 2013-2014 influenza season, a quadrivalent intranasal influenza vaccine containing two A subtypes and two B strains will be available.

Annual influenza vaccination is recommended for all individuals 6 months and older. In addition, children between 6 months and 8 years of age who receive influenza vaccine for the first time should receive two doses in that season, separated by at least 4 weeks (Reference 15). Children between 6 months and 8 years of age who received only one influenza vaccine dose in their first year of vaccination usually require two doses the following season, but if the vaccine strains are the same both years, only one vaccine dose is needed in the second season (Reference 16). Despite its potentially increased efficacy in children, there are currently no patient populations where LAIV is preferred over TIV. The LAIV is indicated only for healthy, nonpregnant patients between 2 and 49 years of age, whereas TIV can be administered to all patients, including those with high-risk conditions. Many manufacturers produce TIV annually, and each product has different age indications. Clinicians should refer to www.cdc.gov/flu on an annual basis for published tables listing influenza vaccine products and the age groups indicated for each vaccine because the products vary each year. Historically, influenza vaccine has been contraindicated in individuals with egg allergies, but recent evidence suggests that TIV can be given safely to these patients, and ACIP recommends giving TIV to patients with egg allergies who experience only hives (Reference 16). Individuals who have had a serious reaction to eggs (angioedema, respiratory distress, lightheadedness, recurrent emesis, or required epinephrine or other emergency interventions) should be referred to a health care provider who specializes in allergic conditions before TIV is considered for use.

Hepatitis A Vaccine

Hepatitis A virus causes a self-limiting acute viral hepatitis characterized by fever, malaise, jaundice, and abdominal pain in adults and older children, but it is often asymptomatic in children younger than 6 years. Chronic infection does not occur with hepatitis A virus, and complications leading to death are extremely rare. Young children serve as a reservoir for the virus because of their lack of symptoms and prolonged viral shedding. Infection occurs by the ingestion of contaminated water or food, through the spread to household contacts by the oral-fecal route, or by direct person-to-person contact. Although hepatitis A is highly endemic in most areas of the world, epidemics of infection occur about every 10 years in the United States, with the last rise reported in 1989 (Reference 1). An estimated 270,000 infections occur annually when asymptomatic infections are considered (Reference 17). Children between 2 months and 18 years of age and people living in Western states have the highest infection rates. Hepatitis A vaccine, introduced in 1995, initially targeted high-risk groups such as international travelers. In 1999, hepatitis A vaccine was recommended for children 2 years and older who lived in areas where hepatitis A rates were twice the U.S. average. Successful reductions in hepatitis A infection rates in these geographic areas led to an expanded recommendation to vaccinate all children (Reference 17).

Hepatitis A vaccine is an inactivated whole-virus vaccine that is available in two pediatric formulations as a single-virus vaccine (Havrix and Vaqta). The two-dose series should begin at 12 months of age, with the second dose given 6–18 months later. The single-virus vaccines are considered interchangeable. Hepatitis A vaccine is also available in combination with hepatitis B vaccine (as Twinrix; refer to Combination Vaccines section and Table 2), but it is only approved for individuals 18 years and older. In addition to use for routine childhood vaccination, hepatitis A vaccine should be considered for any person 1 year and older who is traveling to a country with high or intermediate endemicity, who will be in close contact with an international adoptee from a country with high or intermediate endemicity, who has a clotting factor disorder, or who has chronic liver disease (References 18, 19).

Measles, Mumps, and Rubella Vaccine

Measles, or rubeola, is a highly contagious viral systemic illness spread through respiratory droplets that leads to viremia and infection of the respiratory tract and other organs. It begins with high temperature, cough, and rhinorrhea before progressing to its characteristic maculopapular rash, which begins at the hairline and spreads downward and outward. Koplik spots, which are pathognomonic for measles, are small blue-white spots that appear on the bright red buccal mucosa near the time the rash appears. Complications of measles include diarrhea and otitis media in children, pneumonia, encephalitis, and, rarely, death. Before the measles vaccination, an estimated 3–4 million cases occurred annually in the United States, with more than 50% of cases reported in children 5–9 years of age (Reference 1). After introduction of the measles vaccine in 1963, the incidence dropped by more than 98% to a nadir of about 1500 cases reported in 1983. However, between 1989 and 1991, a resurgence occurred, with a disproportionate number of cases reported in children younger than 5 years. Immunization efforts were subsequently enhanced in preschool-aged children, and measles was declared eliminated in the United States in 2000. However, up to 200 cases per year are still reported annually in the United States because of importation and spread from foreign countries, where unvaccinated travelers contract the infection and spread it to unvaccinated individuals when they return from travel. In 2011, the United States reported 222 measles cases, mainly caused by unvaccinated individuals who traveled to endemic areas or countries experiencing large outbreaks (Reference 20).

Measles vaccine is a live attenuated viral vaccine that is only available in combination with mumps and rubella vaccine (as MMR) or in combination with varicella vaccine (MMRV; refer to Combination Vaccines section and Table 2). After administration, it produces a subclinical and noncommunicable infection that results in immunity in 95% of individuals. A second dose provides immunity to 99% of individuals and forms the basis for the two-dose series recommendation implemented in 1989 (Reference 21).

Mumps is a viral illness spread through respiratory droplets that has a nonspecific prodrome of myalgia, headache, and low-grade fever, followed by its characteristic parotitis in 30% to 40% of cases and aseptic meningitis in up to 15% of cases (Reference 1). Orchitis occurs in up to 50% of postpubertal males, and rare complications include pancreatitis, myocarditis, and deafness. After the mumps vaccine was introduced in 1967, the number of reported cases in the United States dropped by 99% and now averages less than 300 cases per year (Reference 1). However, outbreaks continue to occur, mainly among those who are unvaccinated or have received only one dose of mumps vaccine. Infections have also been reported in fully immunized individuals, which may be a result of antigenic diversity between vaccine and circulating strains.

Mumps vaccine is a live attenuated viral vaccine containing the Jeryl Lynn strain that is only available in combination with measles and rubella vaccine (as MMR) or in combination with varicella vaccine (MMRV; refer to Combination Vaccines section and Table 2). After administration, it produces a subclinical and noncommunicable infection that results in immunity in up to 91% of individuals after one dose, but individuals who receive two doses are better protected during outbreaks (References 21, 22). Two doses of a mumps-containing vaccine are now recommended by ACIP.

Rubella, or German measles, is a viral infection that is often asymptomatic but can cause a maculopapular rash, lymphadenopathy, low-grade fever, and mild respiratory symptoms. It is spread through respiratory droplets that are inhaled or through direct contact with contaminated secretions that reach the mucus membranes. Rubella vaccination was developed to prevent congenital rubella syndrome, which occurred in 25% of infants whose mother was infected during the first trimester of pregnancy (Reference 21). Congenital rubella syndrome is characterized by congenital deafness, cataracts or glaucoma, heart disease, microcephaly and mental retardation, and other organ defects. Rubella acquired during pregnancy can also result in miscarriage or stillbirth. After rubella vaccination began in 1969, there was more than a 98% reduction in all reported rubella cases (Reference 1). It is no longer considered endemic in the United States despite reported outbreaks

that occur mainly among unvaccinated Hispanic populations. About five congenital rubella cases a year have been reported since 1980, and increases generally occur after rubella outbreaks.

Rubella vaccine is a live attenuated viral vaccine that is only available in combination with measles and mumps vaccine (as MMR) or in combination with varicella vaccine (as MMRV; refer to Combination Vaccines section and Table 2). More than 95% of people develop immunity after a single dose of rubella vaccine, and most are protected for at least 15 years (Reference 1). At least one dose of rubella-containing vaccine is recommended to be given at 12 months or older.

The MMR vaccine is given as a two-dose series to elicit an immune response in those who did not respond to the first dose. The first dose should be given no earlier than 12 months of age, and the second dose should be given at 4–6 years of age before the child enters elementary school. The second dose can be given as early as 28 days after the first dose. Children between 6 and 12 months of age who are traveling to endemic areas should be vaccinated before travel, but they must be revaccinated with two doses beginning at 12 months or older. Because MMR contains live viruses, it is contraindicated in pregnancy and immunosuppressed patients, except in asymptomatic or mild HIV infection. Measles can be severe in those infected with HIV, so the benefits outweigh the risks of vaccinating people with asymptomatic or mild HIV infection.

Varicella Vaccine

Varicella is a highly contagious infection caused by varicella zoster virus that is spread by respiratory droplets. Primary infection causes chicken pox characterized by malaise, fever, and characteristic pruritic macules that progress to vesicles, which erupt and crust over during a period of several days (see Skin and Soft Tissue Infections chapter). Secondary bacterial skin infections are a common complication of chicken pox. Adults and immunocompromised individuals have more severe illness, including pneumonia and encephalitis. After the primary infection resolves, the virus becomes dormant in dorsal nerves and can reactivate as herpes zoster, or shingles, creating a pruritic, vesicular rash along a single nerve track. Zoster usually occurs in elderly and immunocompromised individuals after waning immunity to varicella zoster virus. Up to 20% of individuals with zoster develop postherpetic neuralgia, a painful condition that persists for months after the zoster rash resolves. Before the varicella vaccine was introduced in 1995, varicella was endemic in the United States, infecting around 4 million individuals annually, leading to 11,000 hospitalizations and 100 deaths each year (Reference 1). The highest incidence of infection was in children between 1 and 9 years of age, and near-universal infection occurred by adulthood. Routine varicella vaccination has reduced infection rates by 83% to 93% and hospitalizations and deaths by more than 90% (Reference 1). The impact of varicella vaccination on zoster is not known.

Varicella vaccine is a live attenuated viral vaccine given as a two-dose series to enhance immunity and minimize breakthrough disease that occurs after single doses (Reference 23). It is available as a single vaccine or in combination with MMR (as MMRV; refer to Combination Vaccines section and Table 2). The first dose is given at 12–15 months of age with a second dose at 4–6 years of age, but the second dose can be given as early as 3 months after the first dose (for children younger than 13 years) or as early as 4 weeks (for children 13 years and older). Varicella vaccine is contraindicated in pregnancy and immunosuppressed patients, but it should be considered for children with HIV infection whose CD4 cell percentage is at least 15% (Reference 23). Vaccine-strain varicella can be transmitted by individuals post-vaccination, particularly those who develop a rash; these individuals should avoid contact with high-risk people who are not immune to varicella.

Meningococcal Vaccine

N. meningitidis is a common cause of meningitis and sepsis in children and adolescents in the United States. Most invasive infections are caused by five encapsulated strains designated serogroups A, B, C, Y, and W-135. Infection is spread through respiratory droplets or contaminated secretions. Meningococcal sepsis is associated with up to 40% mortality despite antibiotics and supportive therapy, and about 20% of survivors have permanent sequelae including deafness, neurologic damage, or loss of limbs (Reference 1). Meningococcal disease was reported in up to 2800 cases annually in the United States, but rates have dropped, particularly for infections caused by serogroups C and Y among children 11–14 years of age, since the introduction of the routine adolescent meningococcal vaccine (Reference 1). Individuals 18–21 years of age continue to have high infection rates despite routine adolescent vaccination. Frequent outbreaks of meningococcal disease are reported, mainly caused by serogroup C, but outbreaks make up less than 5% of reported cases.

Three inactivated meningococcal vaccines are available, all containing serogroups A, C, Y, and W-135: one polysaccharide vaccine (Menomune; available since 1978) and two conjugate vaccines (Menactra, available in 2005, and Menveo, available in 2010) that incorporate different protein carriers. The polysaccharide vaccine is poorly immunogenic in children younger than 2 years, and it does not produce long-lasting immunity. Use of this vaccine is no longer routinely recommended for children. Both conjugate vaccines are licensed for individuals between 2 and 55 years of age (Menactra is also

approved for children as young as 9 months of age), but antibody levels wane within 3–5 years of vaccination. In addition, a combination vaccine containing *N. meningitidis* serogroups C and Y and conjugated Hib vaccine (Menhibrix; refer to Combination Vaccines section and Table 2) was approved for use in 2012. Routine primary vaccination with a single dose of conjugate vaccine is recommended at 11–12 years of age, with a booster dose at 16 years of age that is expected to provide immunity through the high-risk adolescent and early adult period (Reference 24). A two-dose primary series, separated by 2 months, followed by a booster dose at 16 years of age is recommended for adolescents with HIV infection because their immune response to a single primary dose is insufficient for protection. Similarly, children 2 years and older with persistent terminal complement deficiency or asplenia should receive a two-dose primary series separated by at least 2 months. For these high-risk populations, booster doses should be given every 5 years. All individuals 9 months of age and older who travel to an endemic area should receive a single meningococcal conjugate vaccine dose before travel. Menactra is recommended for children 9–23 months of age who have complement component deficiencies, who are in a defined risk group for outbreaks, or who are traveling to endemic areas. These patients should receive a two-dose series beginning at 9 months of age, with the second dose given at least 3 months after the first dose.

Human Papillomavirus Vaccine

Human papillomavirus (HPV) is the most common sexually transmitted disease in the United States and is associated with genital warts, cervical cancer, and other anogenital cancers. More than 100 different types have been identified, but four types are most commonly found to cause genital warts and cervical cancer. Low-risk types HPV 6 and 11 cause 90% of genital warts, and high-risk types HPV 16 and 18 cause 70% of all cervical cancers (Reference 1). Most HPV infections are asymptomatic, which allows viral propagation to occur among unknowing partners. More than 6 million new infections are estimated to occur annually in the United States, most commonly among adolescents and young adults (Reference 1). Although more than 80% of sexually active women have been infected by 50 years of age, HPV infection occurs in at least 20% of men (Reference 1).

Two inactivated HPV vaccines are available, both containing virus-like particles from types 16 and 18: HPV2 (Cervarix) and HPV4 (Gardasil). The HPV4 vaccine also contains virus-like particles from types 6 and 11. Both vaccines were around 95% effective in preventing precancerous lesions from types 16 and 18 in females who were not infected with these types at the time of vaccination (References 25, 26). The HPV4 vaccine was also shown to protect against 90% of genital warts caused by types 6 and 11. It is ideal to vaccinate before HPV exposure through sexual contact, but sexually active females should still be vaccinated. Routine vaccination with HPV2 or HPV4 is recommended for females in a three-dose series between 9 and 26 years of age; the second and third doses should be given 2 and 6 months after the first dose. When possible, the same HPV vaccine should be given for the entire series. The HPV4 vaccine may be given to males between 9 and 26 years of age in an identical dosing fashion to protect against genital warts (Reference 27).

Combination Vaccines

Combination vaccines reduce the number of injections and increase the chances that the childhood immunization schedule will be completed, particularly for young infants who require several injections at each health encounter. Combination vaccines typically contain components that are given on a similar dosing schedule, and they result in immune responses similar to those of separately administered components. Several combination vaccines are available in the United States, and they have specific administration indications (Table 2). Despite their convenience, these vaccines often cost more than single-component vaccines given separately, and they usually result in higher rates of fever and local skin reactions. One combination vaccine, MMRV, is associated with a higher rate of febrile seizures than MMR and varicella vaccines given separately for the first dose in the series (Reference 28). The ACIP recommends that MMR and varicella vaccines be given separately for the first doses in the series, but MMRV is preferred for the second dose.

Special Populations

Immunocompromised

Immunocompromised hosts benefit from vaccines that provide protection against infection, but an individual's response to a vaccine can be altered if given during an immunosuppressed state. All vaccines should be given before immunosuppression, when possible, and live vaccines should not be given to individuals who are significantly immunocompromised. Live vaccines should not be given to patients within 3 months of chemotherapy or to patients receiving immunosuppressive doses of glucocorticoids (2 mg/kg/day of prednisone or equivalent dose of another steroid for at least 2 weeks) (Reference 29). Live vaccines should not be given post-transplantation to patients with solid-organ transplants, but they can be considered 2 years after hematopoietic stem cell transplantation if the child is believed to be immunocompetent (Reference 29). Inactivated vaccines

may be less effective in these populations, but they can be given when immunocompromise is lessened (i.e., at least 6 months post–solid-organ transplant or at least 12 months post–stem cell transplant; 1 month after discontinuing high-dose steroids) (Reference 29). Household contacts of immunosuppressed individuals should receive all routinely recommended vaccines.

Pregnancy

Women who are trying to become pregnant or who are pregnant should receive all routinely recommended vaccines, when possible, to ensure that sufficient antibodies are passed to the fetus to protect the infant after birth. Live vaccines should not be given during pregnancy to avoid the risk of transplacental infection of the fetus. Inactivated influenza vaccine should be given to women who are or will be pregnant during influenza season. Tetanus, diphtheria, and pertussis vaccines should be given to women before pregnancy, when possible, or immediately postpartum. If protection is needed during pregnancy, Tdap may be given if there is a high risk of pertussis; otherwise, Td is preferred. The HPV vaccine is not recommended during pregnancy, but if it is given to a pregnant woman, it should be reported to the manufacturer's vaccine pregnancy registry.

Vaccine Safety

Vaccinations are one of the most important public health measures used to prevent disease, but they are not completely free of harm. Although most vaccine adverse reactions are acute, mild, and self-limiting, there are sometimes rarely occurring events that are serious and potentially fatal. Many people have not experienced a time when vaccine-preventable diseases were common in children, and the very low but potential risk of harm from vaccines may be perceived to outweigh their benefit. In the United States, vaccine information statements are required to be provided before vaccinations occur to provide information on the risks and benefits of each vaccine. This provides an opportunity for health care providers to discuss vaccine benefits and risks with patients and caregivers. Public education and vaccine safety surveillance are vital to public confidence in vaccines and the subsequent success of immunization programs.

Vaccine safety is monitored by the CDC and FDA through the Vaccine Adverse Event Reporting System (VAERS), a passive reporting system capturing adverse events that can be reported by health care providers, manufacturers, and the public. Reports to VAERS can occur by mail, by fax, or online at http://vaers.hhs.gov. Health care providers are mandated to report specific adverse events that are serious or life threatening. Some vaccine-specific adverse effects are included in Table 1.

Mild Reactions

The most common types of vaccine adverse reactions are local reactions and fever. Pain, swelling, and erythema at the injection site occur after up to 80% of vaccine doses (Reference 1). These reactions are more common with repeated or booster doses because of the presence of preformed antibodies and rapid immune response from previous doses. Local reactions are most common with inactivated adjuvant-containing vaccines, such as those containing diphtheria and tetanus toxoids. Fever, defined as a temperature higher than 100.4°F (38°C), occurs because of cytokine production during the immune response to a vaccine. Fever is most commonly reported after the administration of live virus vaccines. These vaccines can also produce symptoms similar to a mild form of the natural disease they protect against because the administered viruses must replicate to induce immunity. The MMR and varicella vaccines can cause rash and fever within 7–21 days postvaccination, and LAIV can cause mild upper respiratory symptoms similar to the common cold.

Efforts to minimize pain and discomfort from vaccines can benefit both the vaccinee and the parent or caregiver. Effective methods for reducing distress and pain in infants and young children include breastfeeding around the time of vaccination, ingesting 2 mL of 50% sucrose solution 1–2 minutes before vaccination with concomitant pacifier use, holding the child during vaccination, using topical anesthetics such as lidocaine-prilocaine, distracting with toys or videos led by a nurse, or combinations of these interventions (References 2, 30–32). In children 4 years and older, effective methods for reducing distress and pain from vaccines include deep-breathing exercises, child-directed distraction (e.g., music or stories played through headphones), nurse-led distraction, use of topical anesthetics, or combinations of these interventions (References 30, 32). Routine use of acetaminophen or ibuprofen before vaccination is discouraged; this practice does not prevent febrile reactions and may blunt the immune response to vaccines (References 2, 33). These medications can be considered for the treatment of fever or local discomfort that occurs postvaccination.

Thimerosal and Autism

Thimerosal was a commonly used mercury-based vaccine preservative until the late 1990s, when vaccine manufacturers began to produce thimerosal-free products in response to reports that children might receive unacceptably high amounts of mercury through routine vaccines. Methylmercury is neurotoxic at high doses and is found in the environment and in fish; moreover, it accumulates in the body. Ethylmercury is a metabolite of thimerosal whose toxicities are not well studied, but it

has no known limits of exposure and does not accumulate in the body. After concerns arose that thimerosal exposure could cause autism in children, several studies showed that children exposed to thimerosal-containing vaccines did not have a higher autism rate compared with the normal background autism rate, strongly suggesting that there is no association (References 34, 35). Despite a lack of evidence linking thimerosal exposure to autism, all childhood vaccines are now either thimerosal free or contain only trace amounts of mercury (less than 0.3 mcg/0.5 mL), except for the multidose influenza vaccines, which contain 25 mcg of mercury per 0.5 mL.

Syncope

Syncope after vaccination is a rare adverse event that can lead to considerable complications, including skull fracture and intracranial hemorrhage. It is most likely to occur in adolescents within 15 minutes after vaccination with HPV, Tdap, or meningococcal conjugate vaccines (Reference 2). Adolescents should be vaccinated while seated and encouraged to remain seated for 15 minutes after vaccination to minimize injury, should fainting occur.

Precautions and Contraindications

Precautions and contraindications are conditions in which vaccines should not be given to avoid adverse events. Precautions are conditions in which there may be an increased risk or increased severity of an adverse event or when there may be a compromised ability for the vaccine to induce immunity. Vaccination is often deferred in these conditions because such conditions are temporary; in some instances, the health care provider may opt to vaccinate the patient because the benefit outweighs the risk. Common precautions for most vaccines include minor acute illnesses with or without fever and mild to moderate local reactions or febrile response to a previous dose of the vaccine. Contraindications are conditions in which there is an increased risk of a serious adverse event; vaccines are rarely administered when contraindications are present. A contraindication for every vaccine is a severe allergic reaction, such as anaphylaxis, to a previous dose of the vaccine or one of its components. Table 1 lists vaccine-specific precautions and contraindications for childhood and adolescent vaccines.

Table 3. Reliable Vaccine Information Source Web Sites

Web Site	Source	Types of Information
www.aimtoolkit.org	Alliance for Immunization in Michigan (AIM)	Free downloadable information for providers and parents; "quick look" handouts are useful for providers
www.cdc.gov/mmwr	Morbidity and Mortality Weekly Report, Centers for Disease Control and Prevention (CDC)	Advisory Committee on Immunization Practices (ACIP) recommendations and updates; immunization coverage rates and disease activity across the nation; free electronic subscription
www.cdc.gov/vaccines	Vaccines and Immunizations, CDC	Information for providers and parents on immunizations, schedules, safety; links to other Web sites
www.cdc.gov/vaccines/pubs/pinkbook/index.html	Epidemiology and Prevention of Vaccine-Preventable Diseases, CDC	Comprehensive information on vaccine-preventable diseases for providers
www.immunizationinfo.org	National Network for Immunization Information	Science-based and up-to-date information on vaccines for providers, parents, media, and policy-makers
www.immunize.org	Immunization Action Coalition	Free downloadable information for providers and parents; can subscribe to free electronic newsletters
www.vaccine.chop.edu	Vaccine Education Center, Children's Hospital of Philadelphia	Vaccine information for parents and providers
www.vaccinesafety.edu	Institute for Vaccine Safety, Johns Hopkins Bloomberg School of Public Health	Objective and timely information on vaccine safety for providers and parents
http://vaers.hhs.gov/index	Vaccine Adverse Event Reporting System (VAERS), CDC, and U.S. Food and Drug Administration (FDA)	Reportable vaccine adverse events; forms to report adverse events to CDC and FDA; links to other vaccine safety Web sites

Vaccine Information Sources

Health care providers need to stay current with vaccination recommendations and updated schedules to best serve their patients. Many reliable Internet sources are available that provide information on ACIP recommendations, schedules, vaccine safety, and links to other vaccination-related Web sites (Table 3). Many of these sites also provide information for parents or caregivers. Hundreds of Web sites exist that provide incorrect or misleading information on vaccines, so health care providers should direct the public to the proper Web sites for trustworthy vaccine information.

Conclusions

Vaccine-preventable diseases are at or near record low rates in the United States because of the successful implementation of routine childhood vaccinations. Health care providers involved in immunization delivery must be knowledgeable about vaccine schedules and recommendations and must evaluate patients for vaccination needs at every health care encounter. Efforts to educate the public about vaccine effectiveness and safety and successful vaccination programs are vital for maintaining widespread immunization coverage and preventing outbreaks of vaccine-preventable diseases.

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CHAPTER 45

KAWASAKI DISEASE

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LEARNING OBJECTIVES

1. Assess the risk factors and complications associated with Kawasaki disease (KD).
2. Distinguish the clinical and laboratory features between typical and incomplete KD.
3. Develop a pharmacotherapeutic plan that contains drug name, dose, route, and duration for acute treatment to prevent coronary artery aneurysms.
4. Explain the mechanisms and benefits of intravenous immune globulin and aspirin in the treatment of KD.
5. Develop a pharmacotherapeutic plan for refractory KD.

ABBREVIATIONS IN THIS CHAPTER

ALT	Alanine aminotransferase
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
IVIG	Intravenous immune globulin
KD	Kawasaki disease
TNF	Tumor necrosis factor

INTRODUCTION

Kawasaki disease (KD) is a multisystem vasculitis of infancy and early childhood classified as a mucocutaneous lymph node syndrome. It is characterized by fever, pleomorphic rash, and a constellation of other symptoms and laboratory abnormalities suggestive of inflammation. The walls of the blood vessels throughout the body become inflamed in patients with KD. Of particular concern, KD may affect the coronary arteries and thereby progress to serious complications, including coronary artery aneurysms or ectasia, which might result in myocardial infarction or sudden death (Reference 1). In fact, KD is the leading cause of acquired heart disease in children in the United States (Reference 2). Furthermore, the reported mortality and recurrence rates of KD are less than 1% and 2%, respectively (References 3, 4).

The current diagnostic criteria for KD consist of clinical symptoms; therefore, diagnosis can sometimes be challenging because of unusual clinical presentations in certain pediatric patients. Nonetheless, early diagnosis of KD is critical to allow appropriate therapy because prompt treatment initiation has considerably decreased the occurrence of coronary artery aneurysms and associated mortality. The standard therapy for KD consists of intravenous immune globulin (IVIG) and aspirin.

ETIOLOGY

Although the etiology of KD remains unknown, infectious, immunologic, and genetic factors have been implicated to result in the immune-mediated vascular inflammation and damage observed with the disease (References 5, 6). Selective expansion of specific T-cell receptors on monocytes observed in patients with KD suggests this syndrome is caused by superantigen-producing microorganisms (Reference 7). In addition, the clinical manifestations of fever and rash, seasonal increase in disease incidence during winter and spring months, age distribution (i.e., rare occurrence in infants younger than 6 months, possibly because of passive immunity from residual maternal antibodies), spatial and temporal clustering, and laboratory features suggest an infectious cause (References 1, 8, 9).

Because one infectious source has not been identified definitively, KD appears to result from an immunologic response that is elicited by several infecting organisms (Reference 5). Pathologically, neutrophils predominate in the early course of KD (References 10, 11). This is followed by the formation of large mononuclear cells jointly with $CD8^+$ T lymphocytes and immunoglobulin A (IgA) plasma cells to stimulate fibroblastic proliferation (Reference 1). In addition to these cells, macrophages, a unique feature evident in KD unlike in other types of vasculitis, contribute to coronary arteritis (References 1, 12).

The striking increase in occurrences of KD in Asian and Asian-American populations and family members suggests the disease has a genetic predisposition (References 13–15). Several genes have been associated with the development of KD, including a single nucleotide polymorphism of the inositol 1,4,5-trisphosphate 3-kinase C gene on chromosome 19q13.2, an array of human leukocyte antigen (HLA) genes, and the angiotensin-1–converting enzyme gene (References 16–19). Furthermore, an increased risk of coronary artery lesions has been observed in patients with the allelic change on the inositol 1,4,5-trisphosphate 3-kinase C gene, possibly because of their heightened T-cell response.

Ethnicity, age, and male sex are the most common risk factors for developing KD. The epidemiologic variation of this syndrome implicates that ethnicity is one risk factor for KD. The incidence of KD is highest among children of Asian or Pacific Islander descent, followed by non-Hispanic African Americans, Hispanics, and whites, respectively (References 9, 20). Up to 90% of KD cases occur in patients older than 6 months and younger than 5 years (References 21, 22). According to the Centers for Disease Control and Prevention, the estimated annual incidence of KD is 17–27 per 100,000 children younger than 5 years in the United States (References 20, 23). Cases of KD are rarely reported in late childhood (older than 12 years) and adulthood. From the Pediatric Health Information System, the median age at first hospital admission for KD is 3.4 years, with 60% aged 1–4 years (Reference 3). Furthermore, in this study, 60% of the patients were male, another risk factor consistently reported by other studies (References 3, 21, 22).

Clinical Presentation

Three clinical phases—acute, subacute, and convalescent—describe the course of KD (Reference 24). The acute phase is marked by fever that usually persists for 1–2 weeks, together with bilateral, nonexudative conjunctivitis; lip and tongue changes ("strawberry" tongue); swelling and erythema of the hands and feet; polymorphous rash; and cervical lymphadenopathy (Reference 1). The resolution of fever completes this acute phase and denotes the beginning of the subacute phase, which occurs in weeks 2 and 3 after the initial onset of fever (Reference 24). During this phase, patients may experience periungual peeling of fingers and toes, arthritis, arthralgia, diarrhea, vomiting, and thrombocytosis (References 1, 24). Finally, recovery from the clinical symptoms signifies the convalescent phase, which continues until the erythrocyte sedimentation rate (ESR) normalizes (usually during weeks 6–8 of illness) (Reference 24).

Diagnosis

The signs and symptoms associated with KD are nonspecific; thus, diagnosing KD requires the exclusion of other potential diseases that cause similar clinical presentations. The clinical and laboratory criteria for diagnosing KD, created by Tomisaku Kawasaki in 1967 and updated in 2004, are presented in Table 1. Symptoms may not occur simultaneously, necessitating close monitoring while waiting for clinical presentation. Prolonged, unexplained fever for 5 days or more (the most consistent feature) and at least four other primary clinical signs of mucocutaneous inflammation are required for a diagnosis of typical or classic KD (References 1, 25). However, in the presence of coronary artery disease, only four or fewer primary clinical features, together with fever for 5 days or more, are needed for KD diagnosis. In addition, KD can be diagnosed on day 4 of fever or earlier by an expert clinician when four or more primary clinical symptoms are present. Finally, in a young child with unexplained fever for 5 days or more and any of the principal clinical features, KD should be considered.

Table 1. Clinical and Laboratory Signs of Kawasaki Disease (References 1, 25)

Primary Clinical Signs[a,b]	Laboratory Abnormalities
Fever ≥ 5 days	Leukocytosis with neutrophilia
Bilateral, nonexudative conjunctivitis	Normocytic, normochromic anemia (appropriate for age)
Changes in lips and oral cavity (cracked, red lips; strawberry tongue; discrete oral vesicles or ulcers)	Thrombocytosis (≥ 450,000/microliters) after 1–2 weeks of illness onset
Polymorphous rash	Elevated erythrocyte sedimentation rate (ESR, ≥ 40 mm/hour) and/or C-reactive protein (CRP, ≥ 3.0 mg/dL)
Extremity changes (edema of hands and feet; palmar erythema)	Sterile pyuria (≥ 10 white blood cells per high-power field)
Cervical lymphadenopathy	Hypoalbuminemia (≤ 3.0 g/dL)
	Elevated serum aminotransaminases (> 50 units/L)

[a]Persistent episodes of fever for 5 days or more, with four or more primary clinical features, are diagnostic criteria for classic Kawasaki disease. In the presence of coronary artery abnormalities, fever for 5 days or more and only four or fewer primary clinical signs are required for diagnosis of Kawasaki disease. In addition, Kawasaki disease can be diagnosed on day 4 of fever or earlier by an expert clinician when four or more primary clinical symptoms are present.
[b]Other clinical signs include cardiovascular (coronary artery aneurysms, congestive heart failure, myocarditis, pericarditis, and arrhythmias); diarrhea, vomiting, or abdominal pain; arthritis; central nervous system manifestations (irritability and aseptic meningitis); and mild uveitis.

Although laboratory findings are not required for a diagnosis of typical KD, some are highly suggestive of KD and can be useful for ambiguous cases. Markers for systemic inflammation indicative of KD include elevation of acute-phase reactants (e.g., ESR, C-reactive protein [CRP]) and leukocytosis with a left shift in the white blood cell count. Normocytic, normochromic anemia, sterile pyuria, hypoalbuminemia, and thrombocytosis are other laboratory abnormalities observed in patients with KD (Table 1).

Atypical or incomplete KD occurs when the five clinical diagnostic criteria are not fulfilled, commonly observed in infants younger than 12 months (Reference 26). Infants 6 months or younger with unexplained fever for 7 days or more and no other clinical signs should therefore be assessed for incomplete KD. In addition, children older than 5 years are more likely to have incomplete KD than those aged 1–4 years (Reference 27). The use of laboratory findings and echocardiography proves invaluable in the differential diagnostic workup for incomplete KD (Table 1). The American Heart Association and the American Academy of Pediatrics recommend the use of the following laboratory tests: acute-phase reactants (e.g., CRP, ESR), complete blood cell count, urinalysis by clean catch, serum alanine aminotransferase (ALT) level, and serum albumin (Reference 1). Nonetheless, improvement in the diagnosis of incomplete KD is essential to ensure timely treatment with the goal of minimizing cardiac complications.

Complications

Although a self-limiting disease, KD can progress to cardiac complications that can result in significant morbidity and mortality. Cardiac sequelae consist of coronary artery aneurysms, congestive heart failure, myocarditis, pericarditis, and arrhythmias. Extensive coronary artery aneurysms (i.e., 8 mm or more) considerably increase the risk of occlusion and myocardial infarction (Reference 28). Prompt initiation of appropriate therapy, particularly within 10 days of fever onset, may prevent cardiac morbidity progression and mortality (Reference 1). Coronary artery aneurysms, the major cardiac complication, occur in one-fourth of untreated children with KD versus 4% with therapy, emphasizing the importance of adequate treatment (Reference 1). Despite treatment, infants younger than 1 year have the highest risk of developing cardiac complications (Reference 29). Additional risk factors for developing coronary artery lesions include male sex, fever for 14 days or more, hyponatremia (less than 135 mEq/L), anemia (hematocrit less than 35%), leukocytosis (more than 12,000/mm^3), and certain ancestries (American Indians, whites, and non-Hispanics) (References 3, 30, 31). Other complications of KD are peripheral arterial occlusion, painful arthritis or arthralgias usually in the lower extremities, and shock.

Recurrence of KD occurs when the second episode follows the first incident by a minimum of 3 months. The recurrence rate is around 1% to 3%, usually observed within the first 2 years after initial diagnosis (References 22, 30, 32).

Treatment

The severity and range of clinical presentations and potential for serious cardiac complications from KD necessitate hospitalization for diagnostic workup and subsequent treatment. Early diagnosis of KD to allow prompt initiation of appropriate therapy can prevent or ameliorate progression toward cardiac complications, an important goal of therapy. Nonetheless, late diagnosis, defined as more than 10 days after illness onset, has been shown to occur in 16% of patients, especially young infants and incomplete KD cases (Reference 33). Pharmacologic treatment is required for all cases of classic KD as well as for incomplete KD in the presence of an abnormal echocardiograph. Treatment should also be considered in incomplete KD cases without cardiac abnormalities because it may prevent progression to coronary artery aneurysms (Reference 25). Even with adequate treatment, coronary artery aneurysms can still occur in 4% of KD cases (Reference 34).

Pharmacologic Therapy

The goal of pharmacologic treatment during the acute phase is to alleviate inflammation in the coronary artery wall and prevent coronary thrombosis. In children with coronary aneurysms who require long-term treatment, prevention of myocardial ischemia or infarction is another therapeutic goal (Reference 1). Aspirin and IVIG are the mainstays of KD treatment. From guidelines developed by the American Heart Association and the American Academy of Pediatrics, the standard therapy for KD includes a single dose of IVIG and high-dose aspirin initiated as soon as the diagnosis is made or within the first 10 days of illness. Such therapy optimally decreases the risk of developing subsequent coronary artery aneurysms (Table 2) (References 1, 26, 34, 35). Additional IVIG doses may be needed in patients who do not respond (e.g., fail to defervesce) to initial therapy (Reference 1). Long-term use of antiplatelet and/or anticoagulation therapies may be warranted when the risk of thrombotic events is high, particularly in patients with rapidly enlarging coronary aneurysms.

The anti-inflammatory properties of IVIG, possibly derived from cytokine production modulation, enhanced T-cell suppressor activity, and neutralization of bacterial superantigens, help resolve fever and other acute inflammatory processes in response to disease (Reference 1). In addition, IVIG prevents coronary artery aneurysms, improves left ventricular contractility,

Table 2. Treatment of Kawasaki Disease (Reference 1)

Disease Type	Standard Therapy	Additional Therapy	Comment
Newly diagnosed, including incomplete type with cardiac abnormality	IVIG 2 g/kg/day infused over 8–12 hours as a single dose[a,b] PLUS High-dose aspirin 80–100 mg/kg/day orally in four divided doses[a,b] until afebrile for 48–72 hours (or until 14th day of illness), followed by 3–5 mg/kg/day[d] until resolution of acute inflammation markers (total duration ~2 months)[e]	Methylprednisolone 30 mg/kg/day intravenously as a single dose plus standard therapy[c] Ibuprofen 5–10 mg/kg every 6–8 hours or naproxen 10–15 mg/kg/day in two or three divided doses for several weeks can be used for prolonged arthritis or arthralgia[f] Clopidogrel 1 mg/kg/day (maximum 75 mg) once daily if allergic to, or intolerant of, aspirin	IVIG – Toxicities: infusion-related adverse effects, possible transmission of bloodborne pathogens; different brands affect clinical efficacy, but no single product has been proven superior Aspirin – Toxicities: aminotransaminase elevation, transient hearing loss, and Reye syndrome; annual influenza vaccination recommended; avoid aspirin during acute viral illness (varicella and flu); avoid NSAID therapy in combination with low-dose aspirin
Refractory	IVIG 1–2 g/kg/day infused over 8–12 hours as a second dose[a,g]	Methylprednisolone 30 mg/kg/day intravenously over 2 hours for 1–3 days until symptoms resolve[h] Infliximab 5 mg/kg intravenously over 2 hours as a single dose	Methylprednisolone – Toxicities: cardiac arrhythmias, infarction and arrest at high doses and rapid infusion, decreased lymphocyte and monocyte counts, most other adverse effects (including growth suppression, glucose intolerance) are associated with long-term use Infliximab – Toxicities: rash, flushing, pruritus, and other dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis; hepatotoxicity with particular increase in alanine transferases, transient hepatomegaly; anemia

[a]Anti-inflammatory action.
[b]Initiate immediately upon diagnosis in the acute phase to prevent the development of coronary artery aneurysms.
[c]Consider for cases at highest risk of developing coronary artery aneurysms.
[d]Antiplatelet action.
[e]Duration of aspirin can be indefinite in cases with cardiac abnormalities.
[f]Avoid concurrent use of NSAIDs with low-dose aspirin to maximize the antiplatelet cardioprotective effect of aspirin.
[g]Cumulative doses exceeding 4 g/kg have not been studied.
[h]For continued refractory cases after the completion of two courses of IVIG.
IVIG = intravenous immune globulin; NSAID = nonsteroidal anti-inflammatory drug.

and normalizes serum lipoproteins (References 36, 37). A single high-dose infusion of IVIG at 2 g/kg, compared with low doses over 4–5 days, has been shown to produce a greater decrease in the duration of fever and length of hospital stay as well as faster resolution of laboratory findings for acute inflammation (References 35, 38). Ideally, IVIG should be initiated within the first 10 days after initial symptoms, although data that suggest benefit with earlier treatment within 4–6 days are conflicting (References 39, 40). However, patients who receive a diagnosis of KD on day 3 or 4 of illness are most likely to have very severe disease that warrants immediate treatment to prevent coronary aneurysms. In fact, they may require re-treatment with IVIG. In some patients with KD, treatment beyond day 10 of illness may be appropriate, particularly in the presence of persistent fever and abnormal cardiac findings.

Different formulations of IVIG vary in biologic effects because they are from donor plasma that undergoes different sterilization processes (Table 3). The risk of coronary artery aneurysms, resolution of fever, and duration of hospital stay differ with brands of IVIG (References 35, 41, 42). Although different brands of IVIG appear to affect clinical outcome, no one brand has been proven superior. Insufficient efficacy data, concerns for fluid overload, product availability, and cost are reasons against exceeding the recommended dose of 2 g/kg, even though IVIG shows a dose-response effect (Reference 38).

Although it does not appear to decrease the development of coronary abnormalities, the anti-inflammatory and antiplatelet activities of aspirin underscore its role in the treatment of KD. Initially, high-dose aspirin (not to exceed 4 g/day) continued until 48–72 hours after fever resolves is recommended to achieve additive anti-inflammatory effects with IVIG. Alternatively, high-dose aspirin can be continued until 14 days after illness onset, with at least 48–72 hours after fever cessation. This is followed by low-dose aspirin for its antiplatelet effect and is continued until resolution of laboratory markers of acute inflammation, or until 6–8 weeks after illness onset to rule out cardiac abnormalities (Table 2). However, in patients who develop coronary abnormalities, aspirin may be continued indefinitely. Although children given diagnoses of KD have decreased aspirin exposure because of reduced absorption and increased clearance, drug monitoring is not necessary. Aneurysm formation and resolution of fever seem to be unaffected by the use of aspirin alone. In fact, most patients who received a single high dose of IVIG without aspirin experienced resolution of fever within 24 hours after completing therapy (Reference 43). Other antiplatelet drugs, including dipyridamole, ticlopidine, and clopidogrel, have been used in KD (Table 2) (Reference 35). Ibuprofen or naproxen may be used for several weeks to treat prolonged arthritis or arthralgia, if present. However, their use should be avoided during low-dose aspirin therapy because they may interfere with the antiplatelet action of aspirin.

Adding methylprednisolone to standard therapy should be considered in KD cases at high risk of cardiac involvement (Table 2) (Reference 44). Factors contributing to significant risk of cardiac abnormalities include CRP of 7 mg/dL or greater, total bilirubin of 0.9 mg/dL or greater, and aspartate aminotransferase of 200 IU/L or greater (Reference 45).

Refractory Cases

About 10% to 15% of patients treated with standard therapy have persistent or recrudescent fever within 48 hours, placing these patients at a 9-fold increased risk of developing cardiac abnormalities (Reference 29). Fever of any grade is indicative of unresolved vasculitis, and its duration is indicative of coronary artery damage. The risk factors associated with unresponsiveness to standard therapy that therefore necessitate re-treatment are as follows:

- age younger than 1 year,
- early diagnosis with initial treatment after 5 days or less of symptoms,
- bands of 20% or greater, CRP of 8 mg/dL or greater,
- elevation of liver enzymes (ALT of 80 IU/L or greater or γ-glutamyl transferase of 60 IU/L or greater),
- thrombocytopenia (platelet count of 30,000/mm^2 or less), and
- hyponatremia (serum sodium of 133 mmol/L or less) (References 46–49).

To minimize cardiac complications, further therapy should be considered in the presence of any of these risk factors. For patients with persistent or recrudescent fever after receiving standard therapy, additional therapy is necessary and should be initiated at least 36 hours after IVIG completion to allow the exclusion of drug-related fever.

Repeated courses of IVIG or other anti-inflammatory agents for vasculitis, including corticosteroids, inhibitors of tumor necrosis factor (TNF), and plasmapheresis, have been used in refractory cases (Reference 3). In limited studies, re-treatment with a second dose of IVIG 2 g/kg was effective in resolving fever in some patients (References 29, 50, 51). The rationale for re-treatment with IVIG, particularly for the high dose, is because of its dose-response effect (Reference 38). When therapeutic response is not achieved even after two courses of IVIG, methylprednisolone can be used for up to 3 days until symptoms resolve (References 51, 52). For highly resistant KD unresponsive to courses of IVIG and corticosteroids, infliximab (a TNF inhibitor) may be considered (References 53, 54). Other therapies that are not well studied or supported for routine use include pentoxifylline (a methylxanthine that specifically inhibits TNF transcription), plasmapheresis, and cytotoxic agents (cyclophosphamide and cyclosporine) (References 1, 55, 56). Further studies are necessary to understand their benefits in KD, particularly because some of these drugs are associated with significant toxicities.

Surgical intervention may be necessary in some cases, depending on the severity of cardiac abnormalities. Because surgical procedures are beyond the scope of this chapter, more information may be obtained elsewhere (Reference 1).

Prevention of Coronary Thrombosis

In children with coronary involvement, additional medications may be necessary for thrombosis prevention. In fact, another goal of KD management in patients with coronary abnormalities is to prevent thrombosis. Because platelet activation occurs during all phases of disease, antiplatelet therapy becomes crucial at every stage. The use of antiplatelet, anticoagulation, or combination therapies will depend on the degree of coronary involvement. For mild, asymptomatic cases, low-dose aspirin is recommended. The addition of other antiplatelet drugs

Table 3. Intravenous Immune Globulin Product Comparison[a]

	Carimune NF	Flebogamma	Gammagard S/D	Gammagard	Gamunex	Iveegam EN	Octagam	Polygam S/D	Panglobulin NF	Privigen
Formulation	Lyophilized powder	Liquid solution	Freeze–dried concentrate	Liquid solution	Liquid solution	Freeze–dried concentrate	Liquid solution	Freeze–dried concentrate	Lyophilized powder	Liquid solution
Approved indication(s)	Primary immuno–deficiency, idiopathic thrombocytopenic purpura	Primary immuno–deficiency	Kawasaki disease, primary immuno–deficiency, idiopathic thrombocytopenic purpura, B–cell chronic lymphocytic leukemia	Primary immuno–deficiency	Primary immuno–deficiency, idiopathic thrombocytopenic purpura	Kawasaki syndrome, primary immuno–deficiency	Primary immuno–deficiency	Kawasaki disease, primary immuno–deficiency, idiopathic thrombocytopenic purpura, B–cell chronic lymphocytic leukemia	Primary immuno–deficiency, idiopathic thrombocytopenic purpura	Primary immuno–deficiency, chronic idiopathic thrombocytopenic purpura
Pediatric doses studied for Kawasaki disease	N/A	N/A	1000 mg/kg × 1 dose; or 400 mg/kg/day × 4 consecutive days	N/A	N/A	2000 mg/kg × 1 dose; or 400 mg/kg/day × 4 consecutive days	N/A	1000 mg/kg × 1 dose; or 400 mg/kg/day × 4 consecutive days	N/A	N/A
IgA content	1.3 g/L	13 mcg/mL	≤ 2.2 mcg/mL (5% solution)	37 mcg/mL	46 mcg/mL	< 10 mcg/mL	≤ 0.1 mg	≤ 2.2 mcg/mL (5% solution)	1300 mg/mL	≤ 25 mcg/mL (10% solution)
Grams of sucrose per gram of Ig	1.67	0	0	0	0	0	0	0	1.67	0
pH	6.6 ± 0.2	5–6	6.8 ± 0.4	4.6–5.1	4.25	6.4–7.2	5.1–6.0	6.8 ± 0.4	6.6 ± 0.2	4.6–5.0
Osmolality (mOsm/L)	In sterile water: 3% 192; 6% 384; 12% 768 In normal saline: 3% 498; 6% 690; 12% 1074	240–350	636 (5%) 1250 (10%)	240–300	258	< 240	310–380	590 (5%)	384 (6% in sterile water) 576 (9% in sterile water)	240–440
Half–life *(can vary from patient to patient)*	21 days	30 days: 3–week dosing interval 45 days: 4–week dosing interval	37.7 ± 15 days	35 days	> 21 days	23–29 days	40 days	37.7 ± 15 days	21 days	28 days: 3–week dosing interval 45 days: 4–week dosing interval
Gamma globulin content (%)	96	> 99	> 90	> 98	> 98	100	> 96	> 90	> 96	≥ 98

[a]Although products available in the United States are not identical or approved for similar indications, they are generally considered interchangeable. However, some clinically relevant differences may affect product selection (i.e., osmolarity differences, sucrose content, fluid volume, product pH, and IgA content).
Ig = immunoglobulin; N/A = not available.

(e.g., clopidogrel and dipyridamole) to low-dose aspirin to further enhance activity through adenosine-5-diphosphate antagonism may be more effective in moderate cases with evidence of enlarged coronary artery aneurysm (Reference 1).

Anticoagulation therapy, particularly in combination with low-dose aspirin, is indicated when the risk of thrombosis is high, as observed in rapidly enlarging coronary aneurysms with abnormal flow conditions and stenoses at the proximal or distal end of the aneurysms. Warfarin with low-dose aspirin is the most common combination therapy used. The targeted range for warfarin's activity is an international normalized ratio of 2.0–2.5 (Reference 1). Because warfarin's full therapeutic effect may take several days, unfractionated heparin may be initiated first to bridge the gap in therapy. Alternatively, low-molecular-weight heparin may be substituted for warfarin, although it requires subcutaneous injections compared with oral administration of warfarin.

Monitoring of Therapy

The targeted therapeutic outcomes for KD are to achieve defervescence, reverse presenting symptoms, normalize any irregular laboratory tests, prevent cardiac abnormalities, prevent coronary thrombosis, and prevent mortality from myocardial infarction or arrhythmias. Hospitalization is required for diagnostic workup and treatment, especially for IVIG administration. Clinical evaluations for the first 2 months after KD diagnosis are needed to obtain information on changes from baseline presentation and treatment response. To ascertain the degree of cardiac involvement, an echocardiogram should be performed within 2 weeks after fever onset and repeated 6–8 weeks later to confirm therapeutic response (Reference 1). As such, referral to pediatric cardiology is required for all patients with KD, particularly after hospital discharge, for close monitoring. Furthermore, additional echocardiographic evaluations are imperative for children at high risk of cardiac effects, including those with persistent fevers or coronary abnormalities. Follow-up echocardiograms every 1–2 years after diagnosis may be warranted to determine the status (e.g., improving or worsening) of coronary aneurysms and to evaluate for other cardiac conditions, including ventricular dysfunction and pericardial effusions. Long-term management of KD depends on the severity of coronary artery involvement and consists of aspirin therapy, anticoagulation, restriction in physical activity, cardiac evaluation, and echocardiogram (Table 4) (Reference 57).

Overall, IVIG is generally well tolerated and less likely to cause adverse effects if infused at the recommended minimum concentration and infusion rate. Infusion-related reactions consisting of flushing, hypotension, nausea, vomiting, fever, chills, pruritus, malaise, myalgia, and chest tightness have been reported with IVIG administration. These reactions generally occur 30 minutes to 1 hour after initiation of the infusion and usually resolve when the infusion is slowed or temporarily discontinued. Pretreatment with acetaminophen and diphenhydramine may help abate these infusion-related reactions.

Serious adverse effects have been reported with IVIG administration. Anaphylactoid reactions, although rare, are likely to occur in patients who have selective IgA deficiency with serum antibodies to IgA and have not received IVIG within the preceding 8 weeks. Products with the lowest IgA content may be used with caution in these patients (Table 3). In addition, nephrotoxicity, including acute renal failure, as evidenced by increases in serum creatinine and blood urea nitrogen, can occur as soon as 1–2 days after IVIG administration. Reports of renal dysfunction have been mostly associated with the use of IVIG products containing sucrose. Finally, aseptic meningitis syndrome, marked by headache, nuchal rigidity, drowsiness, fever, photophobia, and gastrointestinal intolerance, has been reported from several hours to 2 days after IVIG administration (References 58, 59). Infusion should be ceased in patients displaying aseptic meningitis syndrome or acute hypersensitivity reactions. Epinephrine and diphenhydramine should also be initiated in children with severe hypersensitivity reactions.

Another major concern for the use of IVIG is transmission of bloodborne pathogens, including parvovirus. Once problematic, hepatitis C virus cannot be transmitted under current sterilization methodologies. In addition, antibodies contained in IVIG may interfere with the immune response to certain live virus vaccines (e.g., measles and varicella). As such, these vaccinations should be deferred for at least 11 months in patients receiving IVIG treatment (Reference 60). Repeat immunization is necessary if the live virus vaccine was administered within 14 days before or at the same time of IVIG administration. Other routine childhood vaccinations should be administered, without any alteration, as recommended by the Centers for Disease Control and Prevention.

Patients with KD may be at increased risk of developing adverse effects from aspirin use, consisting of elevation of transaminases, transient hearing loss, and Reye syndrome. Altered protein binding that increases free drug levels as a result of hypoalbuminemia observed in children with KD has been implicated as the potential mechanism for increased toxicity (Reference 44). Children undergoing long-term aspirin therapy should receive their annual influenza vaccine, specifically the inactivated form (Reference 61). Household contacts should also receive their annual influenza vaccine using either the live or inactivated formulations. In addition, aspirin, including the low-dose therapy, should be discontinued in patients with influenza or varicella infection to avoid

Table 4. Long-term Management of Kawasaki Disease (Reference 57)

Type of coronary artery abnormality	Management
No coronary artery abnormality, or transient ectasia/dilatation	• Low-dose aspirin for 2–3 months • Follow up in 1 year and then at 3- to 5-year intervals for assessment of cardiovascular risk • Normal physical activities
Small to medium coronary aneurysm (3–6 mm)	• Low-dose aspirin until regression is documented with echocardiogram • Physical activities should be guided by biennial stress or myocardial perfusion tests for children ≥ 11 years old (no restriction in those < 11 years old)
Large coronary aneurysm (> 6 mm)	• Low-dose aspirin indefinitely • Warfarin therapy with international normalized ratio at 2.0–2.5 (alternative is subcutaneous low-molecular-weight heparin) • Immediate referral to pediatric cardiologist[a] • Cardiac evaluation and echocardiogram every 6 months • Physical activity restricted to stress test results, conducted annually, and level of anticoagulation
Coronary artery obstruction or ischemia	• Evaluate for angioplasty, bypass grafting, stent placement, or cardiac transplantation

[a]Referral to pediatric cardiology is necessary for all patients with Kawasaki disease, particularly after hospital discharge, for close monitoring. However, immediate referral upon diagnosis of Kawasaki disease is necessary for patients who initially present with significant coronary aneurysm.

Reye syndrome. Furthermore, aspirin should be avoided in the 6 weeks after varicella vaccination. Clopidogrel 1 mg/kg/day (maximum 75 mg) can be temporarily substituted for aspirin in these situations, as well as in patients who are allergic to or intolerant of aspirin. Ibuprofen and other NSAIDs (nonsteroidal anti-inflammatory drugs) should be avoided in combination with low-dose aspirin because of their ability to interfere with the antiplatelet cardioprotective action of aspirin.

Adverse effects for other therapies used in KD are provided in Table 2. Further studies are needed to evaluate the role of corticosteroids as a first-line treatment in conjunction with IVIG and aspirin in certain high-risk KD cases. Other agents, including antioxidants and neutrophil elastase inhibitors, are being evaluated for the treatment of refractory KD, but their efficacy remains unclear.

Conclusions

Kawasaki disease is a vasculitis that appears primarily in infancy and early childhood. The current diagnostic criteria for KD consist of clinical symptoms; therefore, diagnosis can sometimes be challenging because of unusual clinical presentations in certain pediatric patients. Aspirin and IVIG are the mainstays of therapy for their anti-inflammatory and antiplatelet effects. Refractory KD cases will require further therapies, including an additional dose of IVIG, corticosteroids, and/or infliximab. Although KD is self-limiting, cardiac complications can occur that can result in significant morbidity and mortality. Prompt diagnosis and treatment of KD with appropriate follow-up monitoring are critical to improve patient outcomes.

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CHAPTER 46

Allergies and Anaphylaxis

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Learning Objectives

1. Describe the incidence of allergic reactions in children, including allergic rhinitis, food allergies, drug-induced allergies, and anaphylaxis.
2. Illustrate the pathophysiology of the various types of allergic reactions.
3. List risk factors for allergic reactions in children.
4. Explain pharmacologic treatment for various types of allergic reactions.
5. Know adverse reactions and limitations of pharmacotherapy for treatment of allergic reactions.

Abbreviations in This Chapter

AR	Allergic rhinitis
FGA	First-generation antihistamine
IgE	Immunoglobulin E
INCS	Intranasal corticosteroid
SGA	Second-generation antihistamine
SJS	Stevens-Johnson syndrome

Introduction

An allergic reaction is defined as an undesired immunologic response to an allergen. Allergic reactions require a previous sensitization to the offending allergen, which on future exposure gives rise to an immunologic-mediated hypersensitivity reaction. Reactions may manifest as a broad spectrum of symptoms from runny nose to gastrointestinal upset to full airway obstruction and death. Allergic diseases in the United States are increasing, especially in children. With such a widespread scope, it is important to recognize and treat the different types of allergic diseases most prevalent in children to minimize their psychological and medical impact. The focus of this chapter will be allergic rhinitis (AR), drug and food allergies, and anaphylaxis.

Epidemiology and Etiology

Allergic rhinitis is the most common allergic disease in children, affecting up to 40% of children in the United States (References 1–3). Allergic rhinitis is an immunoglobulin E (IgE)-mediated inflammatory immune response, usually to inhaled allergens, in the nasal and sinus passageways. Symptoms may appear seasonally or persist year-round, depending on the triggering allergen. Its prevalence is almost nonexistent in children younger than 2 years, but it steadily increases, with bimodal peaks during the early school and adolescent periods. Prevalence decreases with age after adolescence (Reference 4). Box 1 shows other associated risk factors for developing AR.

Allergic rhinitis profoundly affects a child's everyday activities, sleep habits, and quality of life. Children with AR are more likely to experience a variety of cognitive and psychiatric issues including poor concentration, attention-deficit/hyperactivity disorder, poor academic and athletic performance during peak pollen season, and low self-esteem (References 8–13). In older children and adults, anxiety and depression rates are higher among those with AR than among those without (Reference 14). Children with AR are also more likely to suffer from other allergic diseases such as asthma and atopic dermatitis. Although AR is not directly associated with fatal reactions, patients with poorly controlled AR are more likely to experience severe and possibly fatal exacerbations of other allergic conditions such as food allergies and asthma (References 13, 15).

Food allergies also profoundly affect children's lives and well-being. They are the most common cause of anaphylaxis in children (Reference 16). Fear of severe reactions, combined with ubiquitous exposure to possible food allergens, causes a high level of anxiety and the presence of social stigmas around children with food allergies. Food allergies involve an immune response to an ingested food and affect anywhere from 4% to 10% of children in the United States (References 17–22). The

Box 1. Risk factors associated with allergic rhinitis.

- Family history of allergic diseases
- Male sex
- Birth during the pollen season
- Firstborn
- Early introduction of formula and food (< 6 months)
- Early use of antibiotics
- Maternal smoking exposure in the first year of life
- Exposure to indoor allergens (e.g., dust mites, mold)
- Serum IgE > 100 IU/mL before age 6
- Presence of allergen-specific IgE

IgE = immunoglobulin E.
Adapted from References 5–7.

most common food allergens, accounting for more than 85% of children with food allergies, are peanuts (1% to 2% of all children), milk (1.7%), shellfish (1.4%), tree nuts (1%), and eggs (0.8%) (Reference 22). The most common causes of fatal reaction are peanuts (50% to 62%) and tree nuts (15% to 30%) (Reference 23).

The risk of developing food allergies appears to be greatest in children of Asian or African American descent (Reference 22). The presence of another preexisting allergic disease (e.g., AR, asthma, atopic dermatitis) or a biologic parent or sibling with a history of allergic disease is also associated with an increased risk of developing food allergies (Reference 24).

Allergic reactions from drugs are a subset of adverse drug reactions that are immunologically mediated responses. It is important to distinguish the term *allergic drug reaction* from the more general term *adverse drug reaction*, which may or may not be immune-mediated. The incidence of drug allergies in children is likely to be overestimated because both children and their parents are often unaware of the differences (Reference 25). This can lead to the unnecessary exclusion of a drug class that would otherwise be preferred.

The incidence of allergic drug reactions in the pediatric population is unknown. A 10-year retrospective cohort study found that 51% of all pharmacist-reviewed adverse drug events among hospitalized children were of allergic origin or idiosyncratic (Reference 26). The most common causes of adverse drug reactions in this study were antibiotics (33%), narcotic analgesics (12%), anticonvulsants (11%), and anxiolytic agents (10%). Nonsteroidal anti-inflammatory drugs have also been implicated in an elevated risk of developing Stevens-Johnson syndrome (SJS) (Reference 27).

In the most severe allergic reactions, anaphylaxis may develop. A commonly accepted definition of anaphylaxis is lacking, but it generally includes an acute onset of systemic symptoms involving the skin, respiratory compromise, decreased blood pressure, gastrointestinal symptoms, and/or other symptoms of end-organ dysfunction (Reference 28). With the increasing prevalence of all pediatric allergies, it is not surprising that anaphylactic allergic reactions are also rising. The mortality from anaphylactic reactions is low, ranging from 100 to 150 cases in the United States per year. However, anaphylaxis causes more than 30,000 emergency department visits each year (Reference 29). Risks of developing anaphylaxis are highest in males, in adolescents, and in children with several allergic diseases (Reference 22). In a series of epidemiologic evaluations of fatalities from anaphylactic reactions, almost all had a positive history for asthma (References 30–33).

Pathophysiology

Allergic reactions occur through a variety of immunologically mediated mechanisms. Most allergic reactions may be classified as one of four types of hypersensitivity reactions (Table 1). Although type I hypersensitivity is the only type associated with an IgE response to a drug, food, or other allergen, and is equated with allergic reaction, types II–IV are significant causes of adverse drug events (often interpreted as an allergy by parents) and other common "allergies" such as those to metals, gluten, and topical contact with plants.

Type I hypersensitivity reactions are the immediate reactions usually associated with anaphylaxis. Type I hypersensitivity has a 15- to 30-minute onset and is associated with IgE production in response to a particular allergen. The IgE antibody antigen-mediated degranulation of cells releases histamine, which produces cutaneous, gastrointestinal, respiratory, and cardiovascular symptoms such as flushing, nausea, bronchospasm, and hypotension. First exposure to an allergen does not usually produce enough IgE to create a clinical response; therefore, most patients presenting with a type I reaction are sensitized from a previous exposure (Reference 34).

Table 1. Types of Allergic Reactions

Type	Mechanism	Example(s)
I	Allergen binds to specific IgE, which causes degranulation of basophils and mast cells, resulting in release of inflammatory mediators	IgE-mediated anaphylaxis from an antibiotic; localized allergic rhinitis
II	Allergen binds to a cell and elicits an IgG or IgM response to the antigen-cell complex, resulting in cell destruction	Hemolysis secondary to penicillin exposure
III	Antigen-antibody complexes form and deposit on blood vessel walls and in various organs, resulting in complement activation and platelet aggregation	Serum sickness from IVIG
IV	Antigen recognition activates a memory T cell, initiating an inflammatory response	Poison ivy–induced contact dermatitis; gluten sensitivity

IgE = immunoglobulin E; IgG = immunoglobulin G; IgM = immunoglobulin M; IVIG = intravenous immunoglobulin.

Type II hypersensitivity or antibody-dependent cytolytic reactions occur when immunoglobulin M (IgM) and IgG are produced in response to an allergen's binding to a host cell (usually a blood cell). In these cases, the allergen binds as a hapten to a cell and elicits an IgM or IgG response to the allergen-cell complex. For example, penicillin attaches to Coombs-positive red blood cell surface proteins. An IgG then binds to the penicillin and red blood cell protein complex, allowing complement to cross-link and destroy the red blood cell, resulting in hemolytic anemia (References 35, 36). This type of reaction usually targets blood cells and is a common cause of drug-induced agranulocytosis, thrombocytopenia, and hemolytic anemia. The onset of type II hypersensitivity reactions is usually 5–12 hours after drug exposure.

Type III or immune complex hypersensitivities are similar to type II hypersensitivities. In type III, antibody-antigen complexes form and deposit along blood vessels and in various organs and tissues. The complexes may activate complement, cause platelet aggregation, and activate macrophages, all of which result in local tissue damage. Many types of medication-induced kidney and joint damage result from these immune complexes. Examples of these medications include quinine, salicylates, and sulfonamides. Onset is usually 3–8 hours after first exposure but may present as late as 7–10 days.

Type IV, also known as delayed type hypersensitivity, is a reaction caused by memory T-cell recognition of an antigen. Upon antigen recognition, T cells initiate an inflammatory response, resulting in neutrophil and macrophage influx. Onset is 24–48 hours after antigen exposure. Most allergic cutaneous reactions are type IV hypersensitivity reactions. This phenomenon occurs commonly in patients given a β-lactam antibiotic during a concurrent mononucleosis infection (References 22, 36).

Clinical Presentation and Diagnosis

Allergic Rhinitis

Clinical manifestations of AR include conjunctivitis, nasal congestion, rhinorrhea, sneezing, cough, wheezing, or headache. Clinical findings may include dark circles under the eyes from sinus congestion (known as allergic shiners) and nasal creases from frequent rubbing of the nose. Diagnosis is largely based on patient history and physical examination. It can be difficult to differentiate symptoms of allergies from congestion and rhinitis secondary to viral illness. Triggers can often be identified when symptoms present concurrently with pollen seasons or exposure to cockroaches, dust, and pets. Symptoms of rhinitis in children younger than 2 years are rarely allergy based because sensitization to environmental allergens takes at least one or two seasons. Other potential etiologies, such as infection, should be ruled out before considering AR in very young children.

Allergy skin testing may help determine whether a patient's rhinitis is an allergic response and can identify the allergen(s). Skin testing involves introducing an allergen percutaneously by a prick or intracutaneously by intradermal injection. This testing creates an in vivo IgE response on mast cells that releases histamine. This creates a wheal and flare that can be measured. However, patients who take commonly prescribed second-generation antihistamines (SGAs) must discontinue them for at least 10 days before testing, and certain skin conditions (e.g., dermatographia) may affect skin test results.

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines suggest that AR be subdivided as intermittent or persistent disease and as mild or moderate-severe disease based on the frequency and severity of symptoms as a basis for selecting treatment (Table 2) (Reference 37).

Food Allergies

Food allergies can manifest as a wide range of symptoms including dermatitis, emesis, diarrhea, abdominal pain, and anaphylaxis. The diagnosis of food allergies is based mainly on symptomatic reports from parents or a clinical history obtained upon acute presentation. A confirmed diagnosis requires a food challenge, but this is not routinely recommended because of the risk of anaphylaxis. Skin testing is a widely used option and was discussed previously. Assays for testing serum for the presence of allergen-specific IgE is another option for diagnosing food allergies, but these are best used as screening tools because the positive presence of IgE may not indicate a true allergy. A positive result simply implies the patient has been sensitized to the food. Patients may use their serum test results as a guide for avoiding or eliminating certain foods from the diet.

Drug Allergies

Allergic drug reactions can be difficult to diagnose because of their broad and fairly common range of symptoms. However, several criteria may help support an immunologically mediated reaction: (1) the reaction does not resemble the drug's pharmacologic effect; (2) there is a delay, usually ranging from hours to days between the drug exposure and the reaction (unless prior sensitization has occurred, in which case the reaction occurs in minutes to hours); (3) reactions occur with even a small amount of the drug; (4) the symptoms are characteristic of an allergic reaction (e.g., anaphylaxis, pruritus); (5) the reaction resolves after the drug is discontinued; and (6) the reaction can be reproduced on subsequent exposure (Reference 38).

Table 2. Allergic Rhinitis and Its Impact on Asthma Classification of Allergic Rhinitis

Intermittent		**Persistent**
Symptoms occur (one of the following): ▪ < 4 days/week ▪ < 4 weeks/year	*or*	Symptoms occur (*both* of the following): ▪ ≥ 4 days/week ▪ ≥ 4 weeks/year
	and	
Mild		**Moderate-Severe**
All of the following apply: ▪ Normal sleep ▪ No impairment in daily activities, sports, or leisure ▪ No impairment with work or school ▪ No troublesome symptoms	*or*	One or more of the following apply: ▪ Impaired sleep ▪ Impaired daily activities, sports, or leisure ▪ Impaired performance at work or school ▪ Troublesome symptoms

Adapted from Reference 37.

Drug allergies manifest as a wide variety of symptoms that are associated with specific drugs (Table 3). The most common manifestation of an allergic drug reaction is cutaneous. Although most skin reactions are mild, severe and life-threatening cutaneous reactions can occur, usually in the form of SJS or toxic epidermal necrolysis. Stevens-Johnson syndrome is a widespread rash with characteristic blistering of the mucosal membranes. Fever may be present. Toxic epidermal necrolysis is similar to SJS, but it involves the breakdown of skin layers and subsequent blistering and the sloughing of large areas of skin.

Skin testing can be a useful diagnostic tool; however, penicillin is one of the few agents used in the skin test with a well-validated predictive value. Skin testing is most appropriate for patients with a history of severe type I penicillin reactions or a vague history of penicillin reactions. The methods for diagnosing drug allergies are similar to those for food allergies because the diagnosis is based heavily on symptoms at acute presentation and clinical history. Skin testing may assist in diagnosis, but only penicillin and a limited number of other protein-based agents (e.g., insulin) have well-validated predictive values. A positive response to a skin test indicates that the patient has specific IgE antibodies, but its correlation to a clinical allergic reaction is unclear. Assays for the presence of serum IgE are available, but as with food allergies, their clinical application is limited (Reference 39).

Anaphylaxis

Anaphylaxis is a systemic allergic reaction that occurs within minutes to hours after allergen exposure. The more severe the reaction, the more quickly it will occur. The first signs are often warm skin with flushing, itching, and a tingling sensation. Skin examination reveals the classic wheal and flare associated with urticaria. In mild reactions, the skin is often the only organ involved. The upper airway is the second most commonly involved organ, especially if the patient also suffers from AR or asthma. Angioedema of the tongue, pharynx, larynx, and uvula can lead to shortness of breath, voice hoarseness, and rarely apnea.

Symptoms of wheezing and airway edema occur as the reaction progresses to the lower airways. Patients with underlying asthma have more severe bronchoconstriction and lower airway symptoms. A similar process of intestinal edema can result in nausea, vomiting, and abdominal pain. Tachycardia or cardiac arrhythmias may manifest with dizziness and chest pain. Even after initial symptoms resolve, in severe cases a biphasic response can occur 6–8 hours after allergen exposure. Therefore, after any anaphylactic event, the patient should be closely observed for at least 6 hours. Rapid decline in blood pressure is the most worrisome complication of anaphylaxis. Patients can experience rapid vasodilation and collapse of the circulatory system. Most fatal anaphylactic reactions occur within minutes of exposure and involve laryngeal or pulmonary edema.

Diagnosis is primarily based on history and physical examination; however, some laboratory tests can aid in diagnosis. Serum tryptase, a mediator released from mast cells, is elevated in anaphylaxis. Blood should be drawn within 6 hours of symptom onset because tryptase has a 2- to 6-hour half-life. Histamine and *N*-methylhistamine can be measured in urine samples several hours after symptom onset. Plasma histamine is not practical to measure because its half-life is about 2 minutes. Identifying the causative allergen is very important to patient education on avoiding triggers. In rare cases of idiopathic anaphylaxis, the causative agent is never identified, yet these patients often have a history of atopy.

Table 3. Common Manifestations of Drug Allergies

Manifestation	Clinical Symptoms	Common Causative Agents
Anaphylaxis (type I reactions)	A rapid onset of cutaneous symptoms associated with respiratory compromise, low blood pressure, and/or persistent gastrointestinal symptoms	Penicillins, cephalosporins
Serum sickness (type III reactions)	Fever, malaise, and lymphadenopathy occurring 1–2 weeks after drug exposure. Cutaneous symptoms such urticaria and rash may/may not be present.	Penicillins, sulfonamides, cephalosporins, radiocontrast dyes
Drug-induced autoimmune disorders (hemolytic anemia, nephritis, hepatitis) (type II reactions)	Arthralgias, myalgias, polyarthritis, and specific organ involvement (e.g., proteinuria, elevated transaminases, jaundice)	Phenytoin, penicillin, sulfonamides
Respiratory	Rhinitis, asthma	NSAIDs, aspirin
Cutaneous	Mild to severe rash, blistering of the mucosal membranes	Penicillins, cephalosporins, NSAIDs, phenytoin, carbamazepine

NSAIDs = nonsteroidal anti-inflammatory drugs.

Treatment

Allergic Rhinitis

The goal of AR treatment is to minimize or prevent symptoms so that quality of life and cognitive function are improved. Initial treatment of AR should always be removing or avoiding the offending allergen. This can be managed by performing more frequent and thorough household cleanings, remaining indoors as much as reasonably possible during peak pollen seasons, and avoiding pets, cigarette smoke, perfumes, and poor air-quality conditions (Reference 40). Box 2 lists avoidance techniques for common specific allergens. Although these are likely the safest and most cost-effective options for managing allergies, they require significant lifestyle changes for both patients and their families.

The histamine-1 (H1)-antihistamines (e.g. diphenhydramine) function as direct competitive inhibitors between histamine and the H1-receptors. The H1-antihistamines are effective, inexpensive, and convenient therapy for alleviating the sneezing, itching, rhinorrhea, and conjunctival symptoms of AR. For children with only mild, intermittent symptoms of AR, H1-antihistamines are preferred on an as-needed basis. Nonsedating second-generation antihistamines (SGAs), such as loratidine, cetirizine, and fexofenadine, are strongly preferred over first-generation antihistamines (FGAs) (References 42, 43). The sedating effects of the FGAs can further diminish cognitive function in children affected with AR (Reference 42). If symptoms are present for more than 4 days/week or for more than 4 weeks/year, or if they begin to affect daily activities, advancing therapy should be considered. See Table 4 for an algorithm on the ARIA guidelines for AR treatment. Dosing recommendations for the various antihistamines are found in Table 5.

First-generation antihistamines have a significant adverse effect profile because they are lipophilic and readily cross the blood-brain barrier, resulting in sedation and cognitive impairment. They are also powerful anticholinergic agents that help alleviate symptoms such as runny, watery nose and eyes, but can cause other undesired effects such as sedation, difficulty urinating, constipation, and dry mouth. A paradoxical hyperstimulation, in addition to seizures, arrhythmias, and apnea, has led the U.S. Food and Drug Administration to recommend that over-the-counter cough and cold medications, including antihistamines, not be used in children younger than 2 years. Manufacturers of some over-the-counter cough and cold medications have taken this recommendation a step further, in accordance with the American Academy of Pediatrics' stricter position, and labeled these products as not for use in children younger than 4 years. First-generation antihistamines should not be used to sedate or promote sleep in children younger than 12 years. For the adolescent population, it is important to educate patients and parents about associated residual daytime sedation caused by a slow elimination of active metabolites.

Second-generation antihistamines are generally preferred over FGAs because they do not have the same central nervous system effects. They are lipophobic, thereby limiting penetration across the blood-brain barrier. Second-generation antihistamines are also preferred

Box 2. Avoidance techniques for common allergens that cause allergic rhinitis.

Pollen

- Stay inside and keep windows and doors closed during the pollen season.
- Shower and wash clothes after outdoor activities.
- Dry clothes and bedding indoors.

Mold

- Clean indoor moldy surfaces with 5% bleach; then dry thoroughly.
- Keep damp areas of the house well ventilated and clean regularly.
- Fix and seal all leaky faucets and pipes.
- Avoid carpet on concrete or damp floors.

Dust Mites

- Use "allergen-proof" covers on all pillows, mattresses, and box springs.
- Wash bedding in hot water (at least 130°F) weekly.
- Maintain an indoor humidity < 50%.
- Remove or minimize carpets and/or upholstered furniture in bedrooms.
- Wash or dry clean throw rugs on a regular basis.
- Remove or minimize any stuffed animals or toys.
- Use a vacuum with a HEPA (high-efficiency particulate air) filter or a double-layer bag.

Animals

- Remove the pet from the home, if possible.
- Do not allow pets into bedrooms.
- If possible, do not allow pet on/near carpet or upholstered furniture.
- Have a nonallergic relative clean the animal's house, litter box, and/or cage.

Cockroaches

- Seal off any area where a cockroach could potentially enter the home.
- Fix and seal all leaky faucets and pipes.
- Keep food and garbage in tightly sealed containers and put pet food away as soon as pets are finished eating.
- Take out garbage and recyclables regularly.
- Wash dishes immediately after use.
- Clean under stoves, refrigerators, and toasters regularly. Wipe off all kitchen surfaces on a regular basis.

Smoke

- Avoid smoking during pregnancy.
- Do not allow smoking inside the house or car.
- Do not allow smoking around the allergic child.
- Avoid wood-burning stoves, fireplaces, or fires.

Insect Stings

- Stay away from nests.
- Have any nests around the home destroyed.
- Remain calm and move away slowly if stinging insects are close by.
- Avoid brightly colored clothing and perfume.
- Keep food and drinks covered outdoors.
- Avoid loose-fitting clothes, open-toed shoes, or going barefoot.

Adapted from Reference 41.

Table 4. Algorithm for Allergic Rhinitis Treatment

Intermittent Allergic Rhinitis		Persistent Allergic Rhinitis	
Mild	**Moderate-Severe**	**Mild**	**Moderate-Severe**
Allergen avoidance	Allergen avoidance		
Select one or more of the following based on symptoms and tolerability: ▪ Antihistamine (oral or nasal) or leukotriene inhibitor ▪ Mast cell stabilizer	Intranasal corticosteroid ± antihistamine (second-generation or nasal) or leukotriene inhibitor If nasal congestion, consider a short-term nasal decongestant. If rhinorrhea, consider ipratropium. If conjunctivitis, consider an intraocular agent based on symptoms.		
If conjunctivitis, consider an intraocular agent based on symptoms	Consider immunotherapy if (any of the following): ▪ prolonged season or symptoms induced by succeeding pollen seasons ▪ lower airway symptoms ▪ insufficiently controlled symptoms on maximal therapy ▪ patient does not want to be on constant or long-term pharmacotherapy ▪ pharmacotherapy induces undesirable adverse effects Consider omalizumab if ≥ 12 years, nonresponsive to previous therapies, and/or immunotherapy is undesirable.		

Adapted from References 37, 43.

over the FGAs because they can be dosed less frequently. Cost can be a deterrent with the SGAs, however, because they are considerably more expensive than the FGAs.

Because neither FGAs nor SGAs affect nasal congestion, both are less effective as monotherapy than intranasal corticosteroids (INCSs). Second-generation antihistamines may be used as a primary therapy for mild, intermittent AR but should be reserved as an adjunctive treatment for moderate-severe intermittent or mild-severe persistent symptoms. The evidence is unclear whether an H_1-antihistamine in addition to an INCS offers more effective symptom management than an INCS alone, and the decision to add one of these agents should be based on a patient's symptoms and tolerance.

An intranasal antihistamine spray (azelastine or olopatadine) offers an alternative route of administration if a child does not tolerate oral antihistamines. The adverse effect profile is minimal as long as the drug is not swallowed, although a bitter taste may make it an unattractive option for many children. Intranasal antihistamines are inferior to INCSs as a monotherapy for persistent and/or moderate to severe AR, but they may be considered for mild, intermittent AR (Table 4).

The ARIA guidelines support the use of an INCS as the first-line therapy after allergen avoidance for persistent AR and moderate-severe intermittent AR (Reference 37). The superior efficacy of INCSs over H_1-antihistamines is supported by extensive literature (References 13, 53–55).

Intranasal corticosteroids inhibit the recruitment of inflammatory cells and the release of proinflammatory mediators. Therapy is best initiated before allergen exposure, but if symptoms are already troublesome, the maximal dose for age should be used initially until symptoms are adequately controlled. Once the child's symptoms are controlled, a step-down therapy should be employed to the lowest effective dose. Efficacy does not vary markedly between the various INCSs (Table 5).

Adverse effects of INCSs include mainly local irritation (dryness, burning, and irritation); however, a major concern, especially for the long-term treatment of children, is hypothalamic-pituitary-adrenal axis suppression and growth retardation. Although substantial evidence exists to suggest that these agents have a minimal effect on growth rates, some literature suggests the preferred use of the newer INCSs with low-to-undetectable bioavailability in children to minimize any potential long-term effects (References 13, 56–58). Table 6 lists the bioavailability of available INCSs. Oral corticosteroids carry a significant adverse effect profile and are not preferred for the routine treatment of AR.

Decongestants (such as pseudoephedrine) are highly effective for relieving nasal congestion. They act by vasoconstriction through α-receptor stimulation. Oral

Table 5. Pharmacologic Agents for Allergic Rhinitis Management

Medication	Pediatric Dosing	Adolescent and Adult Dosing
First-Generation Antihistamines		
Brompheniramine	2–5 years: 1 mg PO every 4–6 hours 6–11 years: 2 mg PO every 4–6 hours	≥ 12 years: 4 mg PO every 4–6 hours
Chlorpheniramine maleate	2–5 years: 1 mg PO every 4–6 hours 6–11 years: 2 mg PO every 4–6 hours (not to exceed 12 mg/day) or extended release: 8 mg PO every 12 hours Alternative dosing: 0.35 mg/kg/day PO divided every 4–6 hours	≥ 12 years: 4 mg PO every 4–6 hours or extended release: 8–12 mg PO every 12 hours; not to exceed 24 mg/day
Clemastine fumarate (Tavist)	< 6 years: 0.11–0.34 mg PO every 8–12 hours, not to exceed 1.34 mg/day 6–11 years: 0.34–0.67 mg PO every 12 hours, not to exceed 4.02 mg/day	≥ 12 years: 0.67–1.34 mg PO every 8–12 hours, not to exceed 8.04 mg/day
Diphenhydramine (Benadryl)	2–5 years: 6.25 mg PO/IM/IV every 4–6 hours, not to exceed 37.5 mg/day 6–11 years: 12.5–25 mg PO/IM/IV every 4–6 hours, not to exceed 150 mg/day Alternative dosing: 1 mg/kg PO/IM/IV every 4–6 hours, up to 50 mg/dose	≥ 12 years: 25–50 mg PO/IM/IV every 4–6 hours, not to exceed 300 mg/day
Second-Generation Antihistamines		
Cetirizine (Zyrtec)	6–12 months: 2.5 mg PO once daily 12 months–5 years: 2.5 mg PO every 12–24 hours	≥ 6 years: 5 mg PO every 12–24 hours or 10 mg PO once daily
Desloratadine (Clarinex)	6–11 months: 1 mg PO once daily 1–5 years: 1.25 mg PO once daily 6–11 years: 2.5 mg PO once daily	≥ 12 years: 5 mg PO once daily
Fexofenadine (Allegra)	6–23 months: 15 mg PO every 12 hours 2–11 years: 30 mg PO every 12 hours	≥ 12 years: 60 mg PO every 12 hours or 180 mg PO once daily
Levocetirizine (Xyzal)	6 months–5 years: 1.25 mg PO once daily 6–11 years: 2.5 mg PO once daily	≥ 12 years: 5 mg PO once daily
Loratadine (Claritin)	2–5 years: 5 mg PO daily	≥ 6 years: 10 mg PO once daily
Oral Decongestants		
Pseudoephedrine (Sudafed)	Not recommended for children < 2 years 2–5 years: 15 mg PO every 6 hours, not to exceed 60 mg/day 6–12 years: 30 mg PO every 6 hours, not to exceed 120 mg/day	≥ 12 years: 60 mg PO every 6 hours as needed or extended release: 120 mg PO every 12 hours or 240 mg PO once daily
Phenylephrine (Sudafed PE)	4–6 years: 2.5 mg PO every 4 hours, not to exceed 15 mg/day 7–12 years: 5 mg PO every 4 hours, not to exceed 30 mg/day	≥ 12 years: 10 mg PO every 4 hours, not to exceed 60 mg/day
Topical Decongestants		
Naphazoline 0.05% (AK-Con)	6–12 years: 1 drop or spray in each nostril every 6 hours as needed Therapy should not exceed 3–5 days.	≥ 12 years: 1 or 2 drops or sprays in each nostril every 3–6 hours as needed Therapy should not exceed 3–5 days.
Phenylephrine (Little Noses, Sinex)	0.16% solution: ≥ 6–11 months: 1 or 2 drops in each nostril every 3 hours as needed 0.125% solution: 1–5 years: 2 or 3 drops in each nostril every 4 hours as needed 0.25% solution: 6–11 years: 2 or 3 drops in each nostril every 4 hours as needed Therapy should not exceed 3–5 days.	0.25% to 0.5% solution: ≥ 12 years: 2 or 3 drops or 1 or 2 sprays in each nostril every 4 hours as needed Therapy should not exceed 3–5 days.

(Continued)

Table 5. Pharmacologic Agents for Allergic Rhinitis Management *(Continued)*

Medication	Pediatric Dosing	Adolescent and Adult Dosing
Oxymetazoline 0.05% (Afrin)	≥ 6 years: 2 or 3 drops or sprays in each nostril every 12 hours Therapy should not exceed 3–5 days.	
Xylometazoline 0.1% (Sinusal)	≥ 12 years: 2 or 3 drops into each nostril every 8–10 hours as needed Therapy should not exceed 3–5 days.	
Nasal Corticosteroids		
Beclomethasone (Beconase AQ) 42 mcg/spray	≥ 6 years: 1 or 2 sprays in each nostril every 12 hours After symptoms are controlled, titrate to lowest effective dose.	
Budesonide (Rhinocort Aqua) 32 mcg/spray	6–11 years: 1 or 2 sprays in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.	≥ 12 years: 1–4 sprays in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.
Ciclesonide (Omnaris) 50 mcg/spray	> 6 years: 2 sprays in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.	
Fluticasone propionate (Flonase) 50 mcg/spray	≥ 4 years: 1 or 2 sprays in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.	Adult: 2 sprays in each nostril once daily Alternative dosing: 1 spray in each nostril every 12 hours After symptoms are controlled, titrate to lowest effective dose.
Fluticasone furoate (Veramyst) 27.5 mcg/spray	≥ 2 years: 1 or 2 sprays in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.	
Flunisolide (Nasarel) 29 mcg/spray	6–14 years: 1 spray in each nostril every 8–24 hours Alternative dosing: 2 sprays in each nostril every 12 hours, not to exceed 4 sprays/nostril/day After symptoms are controlled, titrate to lowest effective dose.	≥ 15 years: 2 sprays in each nostril every 8–12 hours, not to exceed 8 sprays/nostril/day After symptoms are controlled, titrate to lowest effective dose.
Mometasone (Nasonex) 50 mcg/spray	2–11 years: 1 spray in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.	≥ 12 years: 2 sprays in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.
Triamcinolone (Nasacort AQ) 55 mcg/spray	2–5 years: 1 spray in each nostril once daily 6–11 years: 1 or 2 sprays in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.	≥ 12 years: 1 or 2 sprays in each nostril once daily After symptoms are controlled, titrate to lowest effective dose.
Nasal Antihistamine		
Azelastine (Astelin) 0.1% intranasal solution	5–11 years: 1 spray in each nostril every 12 hours	≥ 12 years: 1 or 2 sprays in each nostril every 12 hours
Olopatadine (Patanase) 6% intranasal solution	6–11 years: 1 spray in each nostril every 12 hours	≥ 12 years: 2 sprays in each nostril every 12 hours
Nasal Mast Cell Stabilizer		
Cromolyn (NasalCrom)	≥ 2 years: 1 spray in each nostril every 6–8 hours	
Nasal Anticholinergic		
Ipratropium (Atrovent) 0.03%, 0.06%	0.03%: ≥ 6 years: 2 sprays in each nostril every 8–12 hours 0.06%: ≥ 5 years: 2 sprays in each nostril every 6–8 hours	

Medication	Pediatric Dosing	Adolescent and Adult Dosing
Ophthalmic Antihistamines		
Azelastine (Optivar) 0.05% solution	≥ 3 years: 1 drop into each affected eye every 12 hours	
Emedastine (Emadine) 0.05% solution	≥ 3 years: 1 drop into each affected eye up to four times/day	
Ophthalmic Antihistamines/Decongestant Combinations		
Antazoline 0.05% + naphazoline 0.05% (Vasocon-A) solution	≥ 6 years: 1–2 drops into affected eye(s) as needed, not to exceed four times/day	
Pheniramine 0.3% + naphazoline 0.025% (Naphcon-A) solution	≥ 6 years: 1 or 2 drops into affected eye(s) as needed, not to exceed four times/day	
Ophthalmic Antihistamine/Mast Cell Stabilizers		
Ketotifen (Zaditor) 0.025% solution	≥ 3 years: 1 drop into lower conjunctival sac of affected eye(s) twice daily at an interval of 8–12 hours	
Olopatadine 0.1% (Patanol) solution	≥ 3 years: 1 drop into each affected eye twice daily at an interval of 6–8 hours	
Olopatadine 0.2% (Pataday) solution	≥ 3 years: 1 drop into each affected eye once daily	
Ophthalmic Mast Cell Stabilizers		
Cromolyn (Crolom) 4% solution	≥ 4 years: 1 or 2 drops in affected eye(s) every 4–6 hours	
Lodoxamide (Alomide) 0.1% solution	≥ 2 years: 1 or 2 drops in affected eye(s) every 6 hours for up to 3 months	
Nedocromil (Alocril) 2% solution	≥ 3 years: 1 or 2 drops in affected eye(s) every 12 hours	
Pemirolast (Alamast) 0.1% solution	≥ 3 years: 1 or 2 drops in affected eye(s) every 6 hours	
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
Ketorolac (Acular) 0.5% solution	≥ 3 years: 1 drop in affected eye(s) every 6 hours	
Leukotriene Inhibitors		
Montelukast (Singulair)	6 months–5 years: 4 mg PO once daily 6–14 years: 5 mg PO once daily	≥ 15 years: 10 mg PO once daily

IM = intramuscularly; IV = intravenously; PO = orally.
Adapted from References 44–52.

decongestants are widely available over-the-counter both as single agents and combined with antihistamines (Table 5). Because of significant adverse effects (e.g., insomnia, agitation, urinary retention), they are recommended only for the temporary relief of nasal obstruction (References 37, 43). Topical decongestants generally have fewer adverse effects than oral agents, but topical agents should not be used for more than 5 days. Therapy extending beyond 5 days can result in rebound congestion and overall worsening of symptoms.

Mast cell stabilizers are available over-the-counter (as cromolyn nasal spray) and by prescription (as several ophthalmic solutions). They are most effective if initiated before the start of allergen exposure and may take up to 2–4 weeks for full effectiveness if begun after symptoms develop. Their efficacy is less than that of INCSs or antihistamines; they may therefore be an option for children who cannot tolerate these other therapies. In addition, they have an excellent safety profile, causing mainly local irritation; however, their frequent dosing (Table 5) limits their practicality in children.

Table 6. Bioavailability of Intranasal Corticosteroids

Medication	Bioavailability (%)
Beclomethasone	44
Fluticasone propionate	< 2
Flunisolide	50
Triamcinolone	< 1
Mometasone	< 0.1
Ciclesonide	< 1
Budesonide	34
Fluticasone furoate	< 1

Adapted from References 13, 59–62.

Montelukast (Singulair) is the only leukotriene inhibitor approved for treating AR (Table 5). Leukotriene inhibitors are competitive antagonists that prevent the binding of cysteinyl leukotrienes (proinflammatory mediators released by eosinophils and mast cells) to the $CysLT_1$ receptor, thus inhibiting inflammatory reactions in the upper respiratory passageways. Some evidence suggests that leukotriene inhibitors are as efficacious as H_1-antihistamines for relieving nasal symptoms, although less so than INCSs (References 43, 63). They may carry an additional benefit in patients with asthma because they also inhibit airway smooth muscle contraction. Montelukast is generally well tolerated with minimal adverse effects. Its safety in children is well supported, with most adverse effects reported as mild headache, ear infection, and nausea (Reference 56). However, leukotriene inhibitors carry a considerable drug cost, and they are not recommended over an H_1-antihistamine. Some benefit may occur in patients with concomitant asthma, but the role of leukotriene inhibitors in AR has yet to be defined (Reference 43).

Ophthalmic therapies are excellent options for patients with conjunctivitis symptoms (Table 5). They act locally, often with minimal adverse effects aside from local irritation. These are excellent options for children with symptoms limited to the eye area.

Ipratropium (Atrovent) is an anticholinergic agent that relieves rhinorrhea (Table 5). When applied topically, it has an antisecretory effect but does not offer relief for other symptoms. Because ipratropium is a topical agent, it has a minimal adverse effect profile, with the most common adverse effects being epistaxis and nasal dryness.

Immunotherapy should be reserved for patients with severe symptoms not well controlled under standard therapy. It consists of subcutaneous injections or sublingual tablets of diluted allergen extracts given at frequent intervals and increasing in concentration during the course of therapy. Over time, the patient's immune system becomes tolerant of the allergens and stops producing hypersensitivity reactions.

Although well established in adults, the efficacy and safety of immunotherapy is controversial in the pediatric population (Reference 13). Immunotherapy can result in life-threatening anaphylactic reactions, requiring that most treatments be administered in an office setting with an adequate observation period. The ARIA guidelines set the same indications for immunotherapy in both children 5 years or older and adults: patients with symptoms induced predominantly by allergen exposure, patients with a prolonged season or with symptoms induced by succeeding pollen seasons, patients with rhinitis and symptoms from the lower airways during peak allergen exposure, patients in whom antihistamines and moderate-dose topical glucocorticoids insufficiently control symptoms, patients who do not want to be on constant or long-term pharmacotherapy, and patients in whom pharmacotherapy induces undesirable adverse effects (Reference 37). It is important to weigh the benefits and risks of immunotherapy before therapy is initiated. Immunotherapy is a long-term, costly investment; a typical course involves one or two treatments per week for 8–12 weeks and then every 4 weeks for 3–5 years.

A new agent in the treatment of AR, omalizumab (Xolair), is a monoclonal antibody that binds to circulating IgE. The IgE-omalizumab complex cannot interact with mast cells or basophils, thus inhibiting IgE-mediated allergic reactions. Currently, omalizumab has only been studied for AR in adults, but it shows significant efficacy in treating nasal symptoms and improving quality of life. U.S. Food and Drug Administration approval is only for patients 12 years or older. Omalizumab carries a black box warning for potentially life-threatening allergic reactions after any dose, even if there is no history of a reaction. Because of its significant cost and potentially life-threatening allergic reactions, omalizumab should be reserved for patients 12 years or older who have not adequately responded to other AR treatments. More research is required before recommendations can be made for infants and children.

Food Allergies

The goals for managing food allergies are primarily to minimize the effect on quality of life and reduce anxiety. The best treatment is prevention, and children and their parents should receive instruction on the importance of avoiding allergens. Referral to an allergist can assist in specifically identifying the offending food(s), which can help prevent an overly restrictive diet. Consulting with a nutritionist may also help ensure adequate nutrition in conjunction with the dietary limitations.

The focus of pharmacologic treatment is purely symptomatic management (diphenhydramine for hives, for example) because no recommended pharmacologic treatment currently exists for preventing food allergies. Food-induced anaphylactic reactions should be treated as a life-threatening emergency in which treatment is initiated as quickly as possible. The treatment of anaphylaxis is discussed later.

Drug Allergies

The goal of treating allergic drug reactions is symptomatic management. Oral antihistamines can be used for treating cutaneous pruritus and rashes. Topical corticosteroids are an option if the reaction is localized to a small area. Topical steroids should not be used over extensive areas, particularly in children, because of the risk of significant systemic absorption.

Anaphylaxis triggered by any drug should be treated as outlined in the Treatment of Anaphylaxis section that follows. The offending drug should be discontinued immediately. For non-life-threatening reactions, the benefits and risks should be considered before discontinuing the medication.

Ultimately, when a clinician is deciding whether to use an agent to which a patient has a documented or suspected allergy, it is best to consider the severity of the previous reaction, the specific symptoms present during the previous reaction, and the timing of the reaction relative to the trigger exposure. Delayed cutaneous reactions, especially to antibiotics, have a low probability of recurring on rechallenge (References 64, 65).

Anaphylaxis

Promptly initiating treatment is vital to minimizing anaphylactic-related morbidity and preventing death (References 30, 31, 66). If possible, the allergic trigger should be avoided or discontinued as quickly as possible. The primary goal should always be to restore and maintain airway, breathing, and circulation, although the emphasis in this chapter will be on treatments specific to anaphylaxis.

It is also important to consider the possibility of a biphasic anaphylactic reaction. This occurs in up to 20% of anaphylactic cases and can be as severe as the initial reaction (Reference 18). The patient will appear to have recovered from the initial episode and suddenly develop a second acute episode of bronchospasm that does not respond as well to initial therapies. Thus, it is important to observe patients before discharge for at least 4–6 hours with moderate reactions and for up to 8–24 hours with severe refractory reactions (References 67–69).

Epinephrine is well supported as the primary pharmacologic intervention for treating anaphylaxis and should be administered as soon as anaphylaxis is suspected (Table 7) (References 28, 67, 68). Despite strong evidence in favor of using epinephrine, other evidence suggests that this treatment goes vastly underused in both the community and emergency settings, with less than one-half of all anaphylactic cases receiving an epinephrine intramuscular injection (Reference 70). An optimal window for epinephrine administration has not been studied; however, delaying epinephrine treatment may be severely detrimental because the lack of prompt treatment with epinephrine is a major risk factor for anaphylactic-related death (References 30, 31, 66). It is worth noting that delayed epinephrine administration is likely to offer some benefit over no administration, so epinephrine should be given as soon as it becomes available.

Epinephrine's action during anaphylaxis is 3-fold: it is an α_1-agonist causing increased blood pressure and decreased vascular permeability by vasoconstriction of vascular smooth muscle, a β_1-agonist causing increased inotropic and chronotropic effects (increased heart rate and cardiac contractility), and a β_2-agonist resulting in bronchodilation (References 71, 72). Administering intramuscular epinephrine to the anterior lateral thigh is preferred because of its more rapid absorption and attainment of higher peaks compared with subcutaneous injections (References 67, 73). Subcutaneous injection has slow absorption because of local vasoconstriction (Reference 67). Intravenous administration carries a high risk of dosing errors, particularly in children; is not practical in most community settings; and is generally not recommended except when intramuscular epinephrine is ineffective or in an acute care setting with continuous cardiac monitoring (References 67, 74). Epinephrine 1:1000 is dosed at 0.01 mg/kg intravenously/intramuscularly, up to 0.3 mg in children and 0.5 mg in older children and adults. Autoinjectors for intramuscular administration are commercially available in 0.15-mg and 0.3-mg doses. Children who weigh 10–25 kg should receive 0.15 mg, and 0.3 mg is indicated for children weighing 25 kg or more (Reference 34). Several doses may be necessary in severe reactions and can be given every 5–15 minutes, as necessary (References 24, 67). Patient education on using an autoinjector is discussed later in the Patient Education section.

Although β-blocker use is uncommon in the pediatric population, a patient's response to epinephrine could theoretically be reduced if he or she is concomitantly taking β-blockers (References 67, 75). Although largely unsupported in the literature, the use of glucagon in children could be useful if epinephrine is having a reduced effect in a patient known to be using a β-blocker. At high doses, glucagon is thought to produce a positive cardiac inotropic effect independent of β-receptors. The recommended dose in children is a 20- to 30-mcg/kg bolus dose up to a maximum of 1 mg administered

Table 7. Management of Anaphylaxis

First-line Therapies	
Epinephrine IM (autoinjector or 1:1000 solution)	10–25 kg: 0.15 mg IM autoinjector > 25 kg: 0.3 mg IM autoinjector *Alternative: 0.01 mg/kg/dose, maximal dose: 0.5 mg/dose* May repeat every 5–15 minutes as needed
Adjunctive Therapies	
Fluid resuscitation	10–20 mL/kg
Supine position with lower extremities elevated	
Supplemental oxygen	
Glucagon	IV bolus: 20–30 mcg/kg over 5 minutes, maximal dose: 1 mg over 5 minutes ≥ *12 years:* 1–5 mg May follow with a continuous IV infusion of 5–15 mcg/minute
H_1-antihistamines	
Diphenhydramine	1–2 mg/kg/dose PO/IM/IV every 4–6 hours, up to 50-mg/dose
Chlorpheniramine	*2–5 years:* 1 mg PO every 4–6 hours *6–11 years:* 2 mg PO every 4–6 hours ≥ *12 years:* 4 mg PO every 4–6 hours
Cetirizine	*6–12 months:* 2.5 mg PO once daily *12 months–5 years:* 2.5 mg PO every 12–24 hours > *6 years:* 5 mg PO every 12–24 hours or 10 mg PO once daily
Levocetirizine	*6 months–5 years:* 1.25 mg PO once daily *6–11 years:* 2.5 mg PO once daily ≥ *12 years:* 5 mg PO once daily
Loratadine	*2–5 years:* 5 mg PO daily ≥ *6 years:* 10 mg PO once daily
Desloratadine	*6–11 months:* 1 mg PO once daily *1–5 years:* 1.25 mg PO once daily *6–11 years:* 2.5 mg PO once daily ≥ *12 years:* 5 mg PO once daily
Fexofenadine	*6–23 months:* 15 mg PO every 12 hours *2–11 years:* 30 mg PO every 12 hours ≥ *12 years:* 60 mg PO every 12 hours or 180 mg PO once daily
H_2 Antihistamines	
Ranitidine	1–2 mg/kg/dose PO/IV, maximum 150 mg
Short-Acting β-Agonist	
Albuterol nebulized solution	≤ *11 years:* 0.15 mg/kg every 20 minutes × 3 doses; then 0.15–0.3 mg/kg every 1–4 hours, maximum 10 mg/dose ≥ *12 years:* 2.5–5 mg every 20 minutes × 3 doses; then 2.5–10 mg every 1–4 hours *Alternative: 0.5 mg/kg/hour continuous nebulization (Adults: 10–15 mg/hour)*
Albuterol MDI	4–8 puffs every 20 minutes × 3 doses; then every 1–4 hours as needed (same dosing for adults)
Glucocorticoids	
Prednisone	1 mg/kg PO, maximum dose: 80 mg
Methylprednisolone	1 mg/kg IV, maximum dose: 80 mg

H_1 = histamine-1; H_2 = histamine-2; IM = intramuscular; IV = intravenous; MDI = metered dose inhaler; PO = oral.
Adapted from Reference 24.

intravenously over 5 minutes, followed by a continuous infusion of 5–15 mcg/minute titrated to clinical effect (Reference 67). Vomiting is a frequent adverse effect, so the airway should be secured before administration.

Aggressive fluid resuscitation (10–20 mL/kg) with a crystalloid intravenous solution such as 0.9% saline or lactated Ringer's solution may be required to support cardiovascular function if initial doses of epinephrine are ineffective. Other vasopressors, such as dopamine or norepinephrine, may be required if fluid resuscitation and epinephrine are inadequate. Patients should be placed in a supine position with legs raised to maximize blood flow to vital organs (References 28, 67). Supplemental oxygen may also be of use to patients experiencing respiratory symptoms and wheezing. Endotracheal intubation should be employed if the patient is unable to maintain a patent airway.

The H_1-antihistamines are the most commonly used pharmacologic intervention for anaphylaxis, but they are not effective as a primary therapy (Reference 70). These agents have a much slower onset of action than epinephrine and do not affect the life-threatening cardiovascular or pulmonary symptoms of anaphylaxis. The H_1-antihistamines should be used only as an adjuvant therapy for the relief of anaphylactic-related cutaneous and nasal symptoms (e.g., urticarial, flushing, rhinorrhea). Some evidence exists that H_1- and H_2-antihistamines given together are more effective at treating the cutaneous symptoms of anaphylaxis versus H_1-antihistamines alone (References 24, 67, 75). For dosing information on various antihistamines, refer to Table 7.

Inhaled short-acting β-agonists such as albuterol may be used as an adjunct to epinephrine for bronchospasm. However, their efficacy for anaphylaxis is not well supported, and delivery may be impaired in severe reactions.

Glucocorticoids have not been evaluated for use in anaphylactic reactions. Because of their usefulness in other allergic reactions (drug-mediated and AR), however, they are commonly used in treating acute anaphylaxis. Some evidence suggests they help prevent a biphasic reaction, although the evidence is minimal (References 30, 76).

Desensitization

Patients may require treatment with a medication known to induce anaphylaxis. Desensitization can be performed by gradually exposing the patient to small doses of the medication according to a strict protocol. The protocol must be started from the beginning if a dose is missed. The full dose of the medication must be given upon completing the protocol; otherwise, it must be repeated. Ultimately, this desensitization allows the temporary administration of necessary medication with few adverse effects. For initial desensitization, patients must be monitored in an inpatient setting with intravenous access and cardiopulmonary monitoring. Often, after the initial desensitization, patients can be desensitized in an outpatient setting. These protocols are commonly used for patients with cystic fibrosis who are colonized with several drug-resistant organisms for whom maximizing antibiotic choices through desensitization is often the only choice.

Patient Education

For patients who have experienced severe allergic reactions, prevention education for future episodes must be discussed with each patient and caregiver, including day care staff, grandparents, teachers, coaches, and babysitters. This includes a prescription for self-injectable epinephrine and instructions on its use. All patients should have action plans in place at school and extracurricular events. Precautions must be taken to avoid known allergens, and caretakers of children should be aware of this importance.

For patients being treated for milder allergic reactions, education regarding prevention is also vital. For severe reactions, both the child and his or her caregivers should take precautions to avoid known triggers. Even children with a history of only mild allergic reactions should be given a prescription for an epinephrine autoinjector because most severe reactions occur in children with no history of allergy.

Proper education is critical for appropriate and accurate use of an epinephrine autoinjector. Children and their parents should be counseled not to delay injection if anaphylaxis is suspected because delayed injections are associated with worse outcomes. The commercially available autoinjectors are designed to work through clothing, so clothing removal is unnecessary before administration. Doses should only be injected into the outer thigh, never into the buttock. In addition, most of the liquid stays in the autoinjector after administration; thus, even if a decreased amount is not visible, patients should be assured they received the correct dose. It is also important to counsel patients never to put thumbs, fingers, or hands over the orange tip of the autoinjector because accidental injection might occur. If the patient does accidentally inject the liquid into the hands or feet, immediate medical attention should be sought because this may result in local vasoconstriction and loss of blood flow to the affected extremity. Box 3 provides instructions for using an epinephrine autoinjector.

The importance of seeking immediate medical attention should also be stressed, as should the fact that the epinephrine injection is not a replacement for medical evaluation and treatment. Medical attention or 9-1-1 notification should be sought immediately after epinephrine is administered. The patient should bring

Box 3. Instructions for use of an epinephrine autoinjector.

- Flip open the yellow cap of the Epi-Pen or green cap of the Epi-Pen Jr. of the carrier tube.
- Remove the autoinjector from the carrier tube.
- Form a fist around the unit with the orange end pointed downward.
- Pull off the blue safety release. (Do NOT remove the blue safety release until ready to use.)
- Hold the orange tip near the outer thigh.
- Swing and FIRMLY PUSH the orange tip against the outer thigh until a click is heard. The unit should be at a 90 degree angle to the outer thigh.
- Hold FIRMLY against the thigh for about 10 seconds.
- Remove unit from thigh (the orange tip will extend to cover the needle).
- Massage injection area for 10 seconds.

Adapted from Reference 77.

the used autoinjector to the emergency department and alert the medical providers that he or she received a dose of epinephrine.

Patients receiving a prescription or over-the-counter recommendation for a nasal spray should be counseled on appropriate technique. Proper technique can help maximize efficacy and minimize local irritation and adverse effects. Sprays should always be primed before first use or if stored unused for more than 1 week. Patients should blow their noses, if possible, before use. If considerable crusting or mucous is present, patients should be encouraged to use a saline nasal spray or irrigation before using the medication. This will allow a maximum application of spray to the nasal membranes. Sprays should always be directed away from the nasal septum to avoid the risk of perforation and irritation. The patient should breathe gently inward through the nostril after each spray and out through the mouth. Nasal applicators should be wiped clean after use and recapped. Adults should assist young children who may have difficulty with these steps.

Conclusions

Diagnosing AR, drug allergies, and food allergies involves a combination of history and laboratory testing. Drug and food allergies can be managed through recognizing and avoiding triggers. Although AR may be managed through avoiding allergens, it often requires pharmacologic intervention. Pharmacologic treatment of AR should be selected on the basis of a child's specific symptoms and optimized for quality of life. FGA or SGA are first-line agents for the treatment of mild, intermittent allergic rhinitis. INCS should be given to patients with moderate to severe or persistent rhinitis with FGA or SGA added if needed. Other pharmacologic agents may be added to treat specific symptoms as need arises (e.g. ophthalmic agents, nasal decongestants). Finding the most effective combination while minimizing the adverse effects of therapies can be challenging because so many effective pharmacologic options are available for physicians and patients to consider.

The pharmacologic treatment of anaphylaxis is difficult to study in a standardized manner. It is unethical to conduct a placebo-controlled trial of epinephrine administration and dosing; thus, we will continue to use the guidelines established from years of clinical experience. It is important to remember that anaphylaxis is a potentially fatal reaction that may occur within minutes of drug or allergen exposure. Medical treatment should be sought immediately if anaphylaxis is suspected. Intramuscular epinephrine should be administered as soon as possible as prompt delivery results in a dramatic improvement in symptoms and reduced morbidity. In the acute care setting, additional measures such as fluid resuscitation and vasopressor use may be required. Antihistamines (first or second generation) should never be considered a first line agent for anaphylaxis treatment as they have no effect on the life-threatening cardiovascular or pulmonary symptoms. Finally, providing education about avoiding triggers is very important in all allergic diseases, as is ensuring that patients have medications such as epinephrine available and instructions on their proper use.

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PART VII

Hematology/ Oncology

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Section Editor

CHAPTER 47

Pediatric Anemia

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Learning Objectives

1. Compare and contrast the pathophysiology of anemia among the different pediatric populations.
2. Describe special concerns that exist in treating anemia in various pediatric patient populations.
3. Review recommendations for preventing, treating, and monitoring anemia in pediatric patients based on laboratory values.
4. Recommend appropriate drug therapy for correction of microcytic and macrocytic anemia in children.
5. Recognize and manage adverse drug reactions in the treatment of pediatric anemias.

Abbreviations in This Chapter

AAP	American Academy of Pediatrics
CHr	Reticulocyte hemoglobin content
CKD	Chronic kidney disease
DFE	Dietary folate equivalent
EP	Erythrocyte protoporphyrin
IDA	Iron-deficiency anemia
KDOQI	Kidney Disease Outcomes Quality Initiative
MCV	Mean corpuscular volume
RBC	Red blood cell
TSAT	Transferrin saturation

Introduction

Anemia is defined by the World Health Organization (WHO) as a hemoglobin concentration that is 2 SDs or more below the mean value for children of the same age and sex who live at the same altitude. Concomitantly, there is an impaired capacity to transport oxygen (References 1, 2). The Kidney Disease Outcomes Quality Initiative (*KDOQI*) workgroup defines anemia as a hemoglobin value less than 12 g/dL in male patients and less than 11 g/dL in premenopausal women and prepubertal patients (Reference 3).

Children, especially infants and preschool children, are at increased risk of morbidity and mortality related to anemia. Anemia that occurs in the fetal period can lead to low birth weight, which is a strong predictor of infant mortality (Reference 4). During the first year of life, rapid growth and a concomitant increase in the number of red blood cells (RBCs) can bring about a marked decline in hemoglobin concentration (Reference 5). Anemia during peak growth periods can have adverse consequences on neurocognitive development (Reference 6). In addition, data evaluating anemia in developing countries suggest that concomitant illnesses with anemia and malaria infection increase the risk of death in children and that the highest mortality risk occurs in the very young (Reference 4).

Anemia is usually caused by nutritional deficiencies in iron, folate, and/or vitamin B_{12}. Severe inflammation, chronic kidney disease (CKD), or other chronic illnesses can lead to anemia (Reference 7). Deficiencies in vitamin A or copper and exposure to lead can also contribute to the development of anemia. Genetic mutations that are associated with impaired erythropoiesis can also cause anemia. Examples include thalassemia, sickle cell trait, and Fanconi anemia (Reference 1). This chapter will discuss anemia caused by deficiencies in folate, vitamin B_{12}, and iron as well as anemia associated with CKD. The chapter will address the implications of persistent anemia as it pertains to a child's health and describe approaches to the clinical management of the condition.

Epidemiology

Data from the WHO Vitamin and Mineral Nutrition Information System for 1993–2005 showed that 24.8% of the world's population is anemic. The most anemia cases were found among women and young children. Children younger than 5 years had the highest prevalence of anemia at 47.4%, whereas 25.4% of children 5 years or older were reported to be anemic (Reference 7). In the United States, the overall prevalence of anemia has been declining and is much lower than that of the world's population, with all-cause anemia among infants and children being around 3.6%.

Globally, iron-deficiency anemia (IDA) is the most common type of anemia (Reference 1). The prevalence of IDA in the United States has not changed for more than 2 decades. Young children, adolescent girls, and pregnant women continue to have a higher prevalence of IDA than all other age groups (References 8–10). Iron deficiency was reported in 9% of toddlers between 1 and 2 years of age and in 9% to 11% of adolescent girls and women of childbearing age in the National Health

and Nutrition Examination Survey (NHANES) 1988–1994. Iron-deficiency anemia was found in 3% of toddlers and in 2% to 5% of adolescent girls and women of childbearing age (Reference 9). In NHANES 1999–2000, the prevalence of iron deficiency among American children 1–3 years of age was 8%. Risk factors in children for iron deficiency include being of Hispanic ethnicity, being of younger age, and being overweight (Reference 10).

Pediatric epidemiologic data for folate and vitamin B_{12} deficiencies are limited because infants and children are typically not screened for these deficiencies. Folate deficiency among children in Western societies is rare. Its prevalence in American children 4 years and older has decreased from 15.5% to 0.5%. Girls between 12 and 19 years of age are at highest risk of folate deficiency (Reference 11). Data for vitamin B_{12} deficiency among infants and children are lacking. However, one study of newborn screening programs in the United States estimated the incidence of neonatal B_{12} deficiency to be 0.88 per 100,000 newborns (Reference 7).

Pathophysiology of Anemia

The primary function of erythrocytes is to deliver oxygen. Old erythrocytes are replaced by new erythrocytes daily. The average life cycle of a normal RBC is 120 days. The erythrocyte life span seen in neonates is about one-half of this duration at 60–90 days (Reference 12). The process by which new RBCs are formed is called erythropoiesis. Multipotential stem cells undergo two stages to become RBCs, but only one stage is responsive to erythropoietin. This is the stem-and-progenitor cell stage (Reference 12). During erythropoiesis, multipotential stem cells in the bone marrow transform into erythroid progenitor cells. Receptors for erythropoietin are located on the erythroid progenitor cells. Erythropoietin causes differentiation and proliferation of the erythrocyte progenitors to produce billions of new erythrocytes daily (References 12, 13).

Erythropoietin is produced primarily in specialized interstitial cells in the renal cortex (Reference 3). It is also produced, to a lesser extent, by the liver (References 12, 13). Transient blood loss, hemolysis, or anemia leads to a decreased number of circulating RBCs and decreased oxygen delivery to tissues. One source of blood loss that is often not accounted for is frequent phlebotomy. Children are at increased risk of anemia from phlebotomy because of their small body size and small total blood volume (Reference 14). Excessive blood loss from laboratory testing is the leading cause of anemia in critically ill neonates (Reference 15).

The kidneys are extremely sensitive to changes in oxygen supply. Under normal conditions, the body has a basal rate of erythropoietin release. Normal plasma concentration for males ranges from 1 mIU/mL to 21.9 mIU/mL and is 1.2–20.5 mIU/mL for females (Reference 16). Tissue hypoxia leads to an exponential increase in the amount of erythropoietin released. This leads to more erythrocyte progenitors surviving during the stem-and-progenitor cell stage. Erythrocyte production increases, permitting enhanced delivery of oxygen to tissues (Reference 13). When blood is replenished or hypoxia is corrected, a negative feedback signal is created to decrease the release of erythropoietin to baseline concentrations (Reference 13).

Healthy term neonates are born with adequate iron stores for about 4 months of postnatal growth (Reference 17). The hemoglobin content of cord blood in a term infant ranges from 13.7 g/dL to 20.1 g/dL (Reference 18). Cord blood hemoglobin of less than 12.5 g/dL is suggestive of fetal anemia (Reference 4). During the first few days after birth, erythropoiesis is maintained at a low level. Between 9 and 29 days of life, a rapid decline in hemoglobin is observed. This event correlates with an increase in erythropoiesis. The number of bone marrow erythroid cells observed at day 29 of life is more than double the amount seen at day 9 of life. After 29 days of life, erythropoiesis is sustained so that, by day 59 of life, the marrow erythroid cell count reaches 22,000 per cubic millimeter (almost 8 times the value seen at day 9 of life). Erythropoiesis is then adjusted to maintain a constant hemoglobin value of 11–12 g/dL (Reference 5).

In anemic patients, one or more factors that affect the sequence of events required for erythropoiesis may fail. Adequate concentrations of iron, folate, and vitamin B_{12} are required to maintain active erythropoiesis. A deficiency in iron, folate, and vitamin B_{12} can lead to decreased hemoglobin and erythrocyte production, thus causing decreased oxygen delivery to tissues (Reference 3). Folate and vitamin B_{12} are involved in the proliferation and differentiation of immature erythrocytes. They are required for the DNA synthesis that accompanies the production of new erythrocytes (Reference 13). In the presence of kidney disease, erythropoietin production may be impaired. Abnormal hematopoietic tissue can lead to impaired responses to erythropoietin. This contributes to impaired RBC formation (References 3, 17).

Clinical Features and Complications

Children who have anemia may be asymptomatic; however, even with mild anemia, the oxygen transport capacity of the blood is reduced. This can lead to lethargy and decreased physical endurance. Often, the clinical presentation of symptoms is related to the root cause of anemia. Common symptoms of anemia include irritability, lethargy, weakness, tachycardia, and pallor.

Anemic infants may be irritable and have poor oral intake. Severe anemia can lead to impaired growth and development. Decreased attention span has also been reported in children. Serious symptoms include arrhythmia, heart failure, and stroke (Reference 19).

Laboratory Data

Hemoglobin

Hemoglobin testing is the standard surrogate for iron deficiency because of its low cost. However, this test fails to identify individuals with mild iron deficiency. Hemoglobin changes typically do not occur until the late stages of iron deficiency. A diagnosis of iron deficiency is made when iron deficiency is severe enough to cause anemia (Reference 20).

The mean and reference range of hemoglobin in newborns is 16.8 (13.7–20.1) g/dL for both males and females (Reference 18). Neonates born to mothers living in high altitudes typically have higher hemoglobin values. Beginning at around 22 weeks, a 0.64% increase in hematocrit and a 0.21 g/dL increase in hemoglobin have been observed for every week's advance in gestational age. Those born between 35 and 42 weeks' gestational age were found to have a mean hemoglobin value of 18 g/dL (Reference 21). Age-specific mean hemoglobin cutoff values for defining anemia in children are listed in Table 1 (Reference 22).

Table 1. Laboratory Cutoff Values for IDA (Reference 22)

Age	Laboratory Cutoff Value
Hemoglobin	
6 months to < 2 years	11 g/dL
2 to < 5 years	11.1 g/dL
5 to < 8 years	11.5 g/dL
8 to < 12 years	11.9 g/dL
Boys 12 to < 15 years	12.5 g/dL
Girls 12 to < 15 years	11.8 g/dL
Boys 15 to < 18 years	13.3 g/dL
Girls 15 to < 18 years	12 g/dL
MCV	
1–2 years	< 77 fL
3–5 years	< 79 fL
6–11 years	< 80 fL
12–15 years	< 82 fL
> 15 years	< 85 fL

IDA = iron-deficiency anemia; MCV = mean corpuscular volume.

Mean Corpuscular Volume

The type of anemia is often classified by RBC size. Mean corpuscular volume (MCV) is the average size of erythrocytes. Red blood cell size in children varies with age. Thus, it is important to consider physiologic changes in the overall assessment of anemia. Several conditions may cause increases in MCV. A value greater than 100 fL suggests the presence of macrocytic anemia. Macrocytic anemia can sometimes be megaloblastic, with folate deficiency and vitamin B_{12} deficiency being the primary causes (Reference 23).

Around one-third of patients with IDA have a normal MCV (Reference 24). Mean corpuscular volume concentrations typically do not drop below normal range early in iron deficiency. Rather, changes are seen after long-standing deficiency (Reference 3). A peripheral blood smear will provide valuable information regarding the morphology of RBCs and assist with diagnosis (Reference 18). Age-specific mean MCV cutoff values for defining microcytic anemia in children are listed in Table 1 (Reference 22).

Total Reticulocyte Count

The total reticulocyte count is an indirect marker of erythropoietic activity. It helps distinguish anemia caused by hypoproduction versus anemia caused by increased RBC destruction. A low reticulocyte count may suggest an impaired production of RBCs, whereas a sustained high reticulocyte count may indicate active blood loss or increased RBC destruction (Reference 19). During the maturation process, reticulocytes exist in the bone marrow for 3 days before entering the circulation. Once they leave the bone marrow, they spend a day in the peripheral blood before becoming mature erythrocytes. During severe anemia, reticulocytes are released early into the peripheral blood. Early release into the circulation shortens their maturation time in the bone marrow but prolongs the time it takes for the cell to mature in the bloodstream (Reference 3).

Screening

The American Academy of Pediatrics (AAP) recommends routine screening for anemia in all children between 9 and 12 months of age. Additional screening is recommended between 1 and 5 years of age for children with risk factors for IDA. These include lower socioeconomic status, Hispanic ethnicity, history of prematurity or low birth weight, lead exposure, being exclusively breastfed beyond 4 months of age, and having inadequate dietary iron intake (References 7, 25).

Initial laboratory testing should include hemoglobin, hematocrit, and red cell indices as well as a white blood cell count and differential, platelet count, reticulocyte count, and examination of the peripheral blood smear. The need for additional laboratory studies is dictated by the patient's history, the physical examination, and the results of this initial testing (Reference 18).

Normal laboratory values in children vary with age. Some laboratory values differ slightly between the male sex and female sex. Therefore, it is important to compare individual results with population-based mean concentrations observed in children of the same age and sex.

Macrocytic Anemia

Pathogenesis

Folate is a water-soluble compound found in plant and animal tissues. Humans are entirely dependent on dietary sources for this nutrient. Primary sources are raw green leafy vegetables, dried cooked beans, and fortified cereals. Animal sources include the liver and kidney (Reference 26). Cooking causes folate loss; however, the extent of loss depends on the type of food and cooking method (Reference 27).

Vitamin B_{12} is found in animal tissue. Therefore, a diet that is strictly vegetarian without the presence of dairy or eggs does not provide a sufficient amount of vitamin B_{12}. Vitamin B_{12} deficiency and anemia can also result from autoimmune pernicious anemia or from malabsorption after gastric bypass surgery (Reference 7). Pregnant women who adhere to a strictly vegetarian diet or who have had gastric bypass surgery are at risk of vitamin B_{12} deficiency, and they place their fetus at risk of deficiency as well. Adults can withstand long-term vitamin B_{12} deficiency without significant physiologic impairment because reserves can last 3–5 years. In contrast, infants have limited hepatic reserves of this nutrient and thus are sensitive to vitamin B_{12} deficiency (Reference 28).

Folate and vitamin B_{12} are essential nutrients that are vitally important in DNA production. Anemia can occur with a deficiency in either vitamin, but a deficiency in one will alter the metabolism of the other (Reference 28). Interference with DNA synthesis can cause abnormal cell division. Rapidly dividing cells are most affected by impaired DNA synthesis. There is an abundance of large and immature erythroblasts and myeloblasts. These cells are collectively called megaloblasts (Reference 13). Anemia that is caused by a deficiency in either nutrient is called megaloblastic anemia. Folate and/or vitamin B_{12} deficiency anemia can lead to impaired DNA synthesis and increased rates of hematopoietic cell death. The mechanism for this cell death has not been identified. Data from animal models suggest that proerythroblasts undergo programmed cell death before differentiating into reticulocytes. Because these cells are unable to mature before undergoing apoptosis, erythropoiesis under these circumstances is deemed ineffective (Reference 13).

Clinical Features and Complications

Folate

Folate is critically important in children because of its role in nucleic acid synthesis. Deficiency during gestation can adversely affect cell replication and growth. Neural tube defects of the fetus (e.g., anencephaly, encephalocele, and spina bifida cystica) are well-documented consequences of maternal folate deficiency, although the mechanism by which this occurs is not known (Reference 29). No similar strong correlations between maternal folate deficiencies have occurred with other adverse fetal or neonatal outcomes. It has been suggested that maternal folate deficiency increases the risk of certain conditions such as abruptio placentae, preeclampsia, spontaneous abortion, preterm delivery, and low birth weight. Mothers who had megaloblastic anemia while pregnant have a markedly high prevalence of abruptio placentae (Reference 30).

Milk is an important dietary source of folate during the first year of life. Most commercial infant formulas are fortified with folic acid (References 31–34). Human breast milk also contains sufficient concentrations of folate (50 mcg/L) for nursing infants (Reference 35). The vitamin is excreted into breast milk in a constant manner, and it is provided to the infant at the expense of maternal stores. Thus, breastfeeding women are at increased risk of folate deficiency and require additional folate (References 30, 36, 37). Infants who are solely fed goat's milk are at risk of folate deficiency and anemia because this type of milk is naturally low in folate content (6 mcg/L). Children with anemia from folate deficiency may present with pallor, lethargy, and failure to thrive (References 35, 38).

Vitamin B_{12}

Infants fed milk from mothers with adequate vitamin B_{12} status are not at risk of developing vitamin B_{12} deficiency. Vitamin B_{12} composition of breast milk from mothers of term infants is highest in colostrum (0.49 mcg/L). Mature breast milk contains about 0.23 mcg of vitamin B_{12} per liter (Reference 39). Breastfed infants of mothers with vitamin B_{12} deficiency are at risk of severe developmental abnormalities, failure to thrive, and anemia (Reference 36). The mothers may not have clinical symptoms of vitamin B_{12} deficiency, but their infants may develop demyelination lesions. These infants do not have megaloblastic anemia but will present with failure to thrive and have neurologic deficits (Reference 30). These infants may be irritable and have abnormal

reflexes and feeding difficulties. Prolonged vitamin B_{12} deficiency can lead to irreversible neurologic damage (Reference 7). If left untreated, almost all patients who have this anemia will eventually develop some nervous system involvement before death occurs. Vitamin B_{12} deficiency lasting more than 3 months will lead to the development of central nervous system lesions. This type of damage is irreversible (Reference 40).

Prevention

Folate

Dietary folates (from natural sources) are found in a conjugated form in food. This factor contributes to the decreased bioavailability of the nutrient (Reference 41). Dietary folates are also prone to degradation from cooking. Spinach and broccoli have been reported to retain less than one-half the amount of folate after they are boiled (49% and 44%, respectively). The extent of nutrient loss depends on the type of food and the cooking method used (Reference 27).

In 1998, the U.S. Food and Drug Administration (FDA) mandated the fortification of cereal products with 140 mcg of folic acid per 100 g of cereal/grain product. This mandate was targeted toward women of childbearing age to prevent neural tube defects. However, children who consume these products also benefit from folic acid fortification (Reference 42).

The Institute of Medicine provides recommendations for adequate intake and recommended daily allowances (RDAs) of dietary folate. The term *dietary folate equivalent* (DFE) is used to describe the RDA of folate. One microgram of DFE (i.e., natural food folate) is equal to 0.6 mcg of folic acid from fortified foods (Reference 37). When a patient takes folic acid in the form of a tablet supplement, the presence of food will affect the bioavailability of the drug (Reference 41). One microgram of DFE equals 0.5 mcg of folic acid if taken on an empty stomach. However, if the supplement is taken with food, then 1 microgram DFE equals 0.6 mcg of folic acid. The RDA for specified age groups is provided in Table 2 (References 3, 37, 43).

Pregnant and breastfeeding women may increase their folic acid intake through supplements. Supplementation with 400 mcg of folic acid daily in pregnancy in addition to dietary folate intake minimizes the risk of neural tube defects (Reference 37). Lactating mothers require an additional 300 mcg of folic acid daily to maintain adequate serum folate concentrations (Reference 30).

Vitamin B_{12}

The best strategy to prevent vitamin B_{12} deficiency is to encourage individuals to consume an adequate amount of the vitamin in their diet. Foods with the highest vitamin B_{12} content include beef, liver, beef by-products (e.g., blood, bone, edible fats, organs), clams, turkey, and chicken. Beef liver and beef-containing variety meats may contain up to 70.66 mcg of vitamin B_{12} per 3 oz (Reference 26). Fortified foods and oral supplements may be an alternative source of vitamin B_{12} (Reference 44). Fortified ready-to-eat cereals contain up to 6 mcg of vitamin B_{12} per serving (Reference 26). The ideal dose of vitamin B_{12} for supplementation has not been established. Recommended daily allowances for specified age groups are provided in Table 2 (References 3, 37, 43).

Diagnosis

MCV and Peripheral Smear

An MCV greater than 100 fL is a sensitive hematologic marker for folate and vitamin B_{12} deficiency. A peripheral blood smear should be included in the initial workup. The presence of macroovalocytes and hypersegmented neutrophils indicates the presence of megaloblastic anemia (Reference 23).

Table 2. Recommended Daily Allowance (References 3, 37, 43)

Age (years unless specified)	Folate (mcg)[a]	Vitamin B_{12} (mcg)	Iron[b] (mg)	Ascorbic Acid (mg)
0–6 months	65[c] (9.4 mcg/kg)	0.4[c] (0.05 mcg/kg)	0.27 mg/day[c]	40[c]
7–12 months	80[c] (8.8 mcg/kg)	0.5[c] (0.05 mcg/kg)	11	50[c]
1–3	150	0.9	7	15
4–8	200	1.2	10	25
9–13 (males)	300	1.8	8	45
9–13 (females)	300	1.8	8	45
14–18 (males)	400	2.4	11	75
14–18 (females)	400	2.4	15	65

[a]Amount listed as dietary folate equivalents (DFEs).
[b]Elemental iron.
[c]Listed as recommendations for adequate intake.

Folate and Vitamin B_{12}

Folate and vitamin B_{12} assessments may be performed by direct vitamin assays or indirectly by surrogate biochemical markers. Direct assays include serum folate, RBC folate concentrations, and serum vitamin B_{12}. Serum folate readily detects deficiency. It is primarily a reflection of short-term folate balance and is subject to diurnal and prandial variations. Red blood cell folate is a more stable value that more accurately reflects average body folate when that particular population of RBCs was produced (References 45, 46).

Surrogate markers reflect the metabolic function of each vitamin. These markers include homocysteine and methylmalonic acid. They may be used to distinguish between folate and vitamin B_{12} deficiency. Homocysteine is associated with folate and vitamin B_{12} status, and methylmalonic acid is more specific for vitamin B_{12}. Homocysteine is a sulfur-containing amino acid that is present in the body. The breakdown of homocysteine requires the presence of both folate and vitamin B_{12}. Deficiency of either vitamin will lead to increased homocysteine concentrations (References 45, 46). Only vitamin B_{12} deficiency is associated with an elevation in methylmalonic acid concentration. Changes in homocysteine and/or methylmalonic acid are not specific to folic acid or vitamin B_{12} deficiencies. Other diseases (e.g., renal failure, hypothyroidism) may also cause an increase in homocysteine and/or methylmalonic acid (References 45, 46). Laboratory values in these patients must be cautiously interpreted. Direct measurement of vitamin B_{12} and/or folate in conjunction with surrogate markers may provide a better diagnosis for deficiency. Table 3 provides reference ranges for these laboratory values (References 47, 48).

Schilling Test

The Schilling test is used to identify malabsorption of vitamin B_{12}. Fasting patients are given a 1-mcg dose of radioactively labeled synthetic cyanocobalamin. Urine is collected during a 24-hour period. Individuals with malabsorption will have lower concentrations of radioactivity in their urine. This test is rarely used because of the high rate of indeterminate results (References 46, 49). Individuals may have normal test results even if malabsorption of dietary cobalamin is present. Inadequate urine collection is a considerable cause of error. In addition, individuals with renal insufficiency may have delayed excretion of the radioactively labeled cobalamin, thus providing an inaccurate interpretation of the test results (Reference 49).

Treatment

Folate

Oxidative cleavage of dietary folate from cooking creates degradation products that are not active and cannot be converted by the body to active folate. Folate deficiency is treated with folic acid. Folic acid is a synthetic vitamin that is a fully oxidized molecule, and it is more stable than dietary folate. Bioavailability of the synthetic formulation is twice the amount seen with dietary folate (Reference 44). Absorption of folic acid is better at smaller doses. High doses cause oversaturation of GI folate transport pathways, resulting in inefficient absorption (Reference 44). Folic acid is relatively well tolerated, and it may be given orally, intramuscularly, intravenously, or subcutaneously. The injectable form of folic acid is available as sodium folate. Dosage recommendations are 100 mcg/day for infants and 300 mcg/day for children younger than 4 years. Those older than 4 years are given a typical adult dose of 400 mcg/day (Reference 50). An extemporaneously prepared formulation can also be prepared (Reference 50).

Vitamin B_{12}

Vitamin B_{12} deficiency in children in the United States is not common; therefore, cobalamin supplementation is seldom used in this population. When supplementation is required, cyanocobalamin given as intramuscular or subcutaneous injections is the preferred route of administration for pediatric patients. The dose used for children with vitamin B_{12} deficiency is not well established. A starting dose of 0.2 mcg/kg can be used. This dose is given for 2 days and then changed to 1000 mcg/day for the next 5 days. The dosing interval is then extended to weekly administration at a dose of 100 mcg/week.

Table 3. Reference Values for Folate and Vitamin B_{12} Assays and Surrogate Markers (References 47, 48)

Direct Vitamin Assays	Reference Range
Serum vitamin B_{12}	
Newborn	160–1300 pg/mL
Child	200–835 pg/mL
Serum Folate	
Newborn	16–72 ng/mL
Child	4–20 ng/mL
RBC folate	
Newborn	150–200 ng/mL
Infant	74-995 ng/mL
2–16 years old	Greater than 160 ng/mL
Older than 16 years	140–628 ng/mL
Surrogate Markers	
Serum homocysteine	4.6–8.1 micromol/L
Methylmalonic acid	0.05–0.26 micromol/L

RBC = red blood cell.

Treatment spans 1 month. Children who have malabsorptive conditions may require long-term cobalamin therapy. Cobalamin may be given in doses of 100 mcg on a monthly basis. An alternative regimen is 100 mcg/day given for 10–15 days, followed by 100 mcg given once or twice a week for several months. Cyanocobalamin given orally is not recommended because absorption by this route is variable. An intranasal formulation is also available; however, it is not FDA approved for use in children at this time (References 51–53).

Monitoring

All patients should have a baseline complete blood cell count for hemoglobin and MCV measurements, together with a peripheral blood smear. Vitamin B_{12} and folate levels can provide the distinction between folate deficiency and vitamin B_{12} deficiency. Folate therapy should be continued for at least 3–4 weeks until a definite hematologic response is observed (Reference 23). Vitamin B_{12} concentrations and a complete blood cell count should be performed 1 month after the start of cyanocobalamin and every 3–6 months thereafter to determine treatment efficacy (References 52, 53). Once therapy is initiated, it may take 1–4 months to achieve complete recovery of hematologic indices.

Serum potassium and a complete blood cell count are particularly important during the initial treatment of vitamin B_{12} deficiency. Laboratory values should be observed closely during the first 48 hours of treatment. When treating patients with severe vitamin B_{12} deficiency, hypokalemia requiring replacement therapy and thrombocytosis may develop. Hypokalemia is caused by an intracellular shift of potassium after correction of anemia. The condition can be severe and fatal (References 52, 53).

Microcytic Anemia

Pathogenesis

Iron is an essential cofactor for many different cellular processes. It is acquired from dietary sources either as heme or non-heme iron. Heme iron (Fe^{2+}) is primarily from animal sources as hemoglobin and myoglobin. It is well absorbed by the gastrointestinal (GI) tract. Nonheme iron (Fe^{3+}) is free iron and is found in foods such as spinach, beans, enriched cereals, and whole grains (Reference 26). This form of iron is not as efficiently absorbed. For iron to be absorbed, ferric iron (Fe^{3+}) must be reduced by brush border ferrireductases in the GI tract to ferrous iron (Fe^{2+}) (Reference 54).

Iron's ability to accept and donate electrons makes it a useful element biologically. This same characteristic gives iron the capacity to be toxic. Iron can catalyze a reaction that generates free radicals. These free radicals can attack cellular membranes, proteins, and DNA. To prevent free radicals from forming, the body maintains a tight regulation of iron by sequestering most of it within proteins (Reference 54). It is incorporated into hemoglobin, myoglobin, and respiratory enzymes and is needed for oxygen transport (Reference 22).

Transport proteins tightly bind to iron and circulate it throughout the body. Transferrin is the main carrier of iron in the blood. Elemental iron bound to transferrin is a critical source of iron for developing erythroid cells within the bone marrow. Once inside the developing erythroid cell, the iron is cleaved off from transferrin and transported to the mitochondria, where it can be made available for incorporation into the heme molecule (Reference 55).

Most iron found in the body is bound to hemoglobin (Reference 22). Two hundred eighty million hemoglobin molecules are carried in one RBC. Hemoglobin is a tetrameric compound consisting of four polypeptide chains. Mature erythrocytes contain a heme group linked to each of the two alpha and two beta chains. Heme is composed of a porphyrin ring and an iron atom. The atom of iron is chelated at the center of the porphyrin ring. Heme readily binds with oxygen. The resulting oxyhemoglobin gives blood its characteristic red color (Reference 56). Iron found in hemoglobin functions as a carrier of oxygen to the tissues from the lungs (Reference 22).

Iron that is not readily used is complexed to ferritin and hemosiderin for storage within cells. Ferritin and hemosiderin are primarily located within the liver, bone marrow, spleen, and skeletal muscles. In healthy individuals, most stored iron is bound to ferritin (Reference 22).

The body efficiently regulates the processes of erythrocyte formation and destruction. When old RBCs are destroyed, the liberated iron is recycled for incorporation back into the hemoglobin. Under normal physiologic conditions, plasma iron concentrations are maintained in a relatively constant range. The balance between concentrations of iron available for incorporation into hemoglobin and those found in storage compartments is efficiently managed (Reference 57). Certain circumstances can tip this balance. Iron deficiency can cause hemoglobin synthesis to slow down and impair erythropoiesis. Fewer reticulocytes may be released by the bone marrow. The reticulocytes that are released are small with decreased hemoglobin concentration. Erythrocytes are described as hypochromic and microcytic.

Iron status has been described as a continuum. Individuals may have normal functional iron (e.g., bound to hemoglobin, myoglobin, and respiratory enzymes) with varying concentrations of transport and stored iron. Persistent iron deficiency may result in severe reductions in total body iron concentrations. Iron depletion exists when the amount of stored iron is reduced but the

amount of functional iron and transport iron is normal. The body may not have sufficient iron stores to mobilize if there is an increased need. With iron depletion, there are no physiologic impairments. Iron-deficient erythropoiesis may occur if the body continues to have a negative iron balance for a sufficient duration. The amount of iron absorbed by the GI tract is insufficient to replace the quantity that is lost, or the body is unable to meet the demands necessary for growth and function (Reference 22). In children, rapid growth can overwhelm the body's ability to maintain sufficient iron concentrations (Reference 54). Adolescent girls, similar to adult women, can become iron deficient because of regular blood loss during menstruation and limited dietary iron consumption (References 8, 58). Iron-deficient erythropoiesis is characterized by depleted iron stores and a reduced transport of iron. The concentration of functional iron is normal. The decreased concentrations of iron will lead to impaired hemoglobin and RBC production. Although iron deficiency is less severe, it still has the potential for causing physiologic impairment. Iron-deficiency anemia is a more severe form of iron deficiency in which functional, transport, and stored iron concentrations are all reduced. The lack of iron leads to an impaired production of hemoglobin, myoglobin, and respiratory enzymes. Red blood cell formation decreases, and organ systems can be adversely affected (Reference 22).

Risk factors for developing IDA in infants include premature birth, low birth weight, and prolonged stay in the neonatal intensive care unit. Preterm neonates possess lower total body iron than term neonates; however, the proportion of iron to body weight is similar between the two populations. The faster rate of postnatal growth experienced by infants who are born premature places them at risk of rapidly depleting iron stores compared with their term counterparts. In these infants, iron deficiency can develop by 2–3 months of age if adequate iron supplementation is not provided (Reference 59).

Infants who are exclusively breastfed and who do not receive iron supplementation are at increased risk of developing anemia (Reference 24). Babies who are not fed iron-fortified formula during the first year of life and those who have an early introduction of cow's milk are also at increased risk (Reference 24). Human breast milk and cow's milk have similarly low concentrations of elemental iron, about 0.5–1 mg/L (References 22, 60). However, human breast milk's bioavailability is around 50% compared with 10% with cow's milk (References 22, 59–62). High calcium and casein content of cow's milk can inhibit GI iron absorption (References 59, 61). In addition, early introduction of cow's milk during infancy can cause occult bleeding from the GI tract (References 62, 63). These factors can contribute to iron loss.

Clinical Features and Complications

Women who are iron deficient early during pregnancy are at greater risk of having preterm delivery and of giving birth to babies with low birth weight (Reference 64). Data suggest that maternal IDA during the first half of pregnancy is associated with an increased risk of preterm delivery, despite correction of iron deficiency during the third trimester. Pregnant women who present with IDA at their first prenatal visit are more likely to give birth to a baby with low birth weight. The risk is 3 times greater if the woman is from a low-income household. The association between premature delivery and low birth weight has not been found with other types of maternal anemia (Reference 65).

Strong evidence supports the role of iron in neurologic development. Some data support the causality of IDA with poor cognitive, neurologic, and motor development. Infants with IDA have lower motor function scores than infants who do not have IDA (Reference 66). Some effects of IDA can be long lasting and irreversible (References 7, 67). Studies evaluating the long-term effects of IDA have reported lower IQ scores for children between 4 and 7 years of age if they had IDA during the first year. One follow-up study that evaluated 167 children from Costa Rica found that infants with severe and chronic IDA still had lower motor scores as well as lower achievement in math and writing in adolescence (Reference 6).

Prevention

The Department of Health and Human Services Healthy People 2010 includes objectives for reducing iron deficiency to less than 5% for children 1–2 years of age, less than 1% for children 3–4 years of age, and less than 7% for females of childbearing age. The AAP has published guidance regarding the diagnosis and prevention of IDA. It is recommended that all preterm infants receive 2 mg of elemental iron per kilogram of body weight per day, the amount provided in iron-fortified formulas. This should be provided through 12 months of age. Preterm infants who are solely breastfed should be given oral iron supplementation by 1 month of age at a dose of 2 mg of elemental iron per kilogram per day. This therapy should be continued until the infant is weaned to iron-fortified formula or is able to consume foods that supply 2 mg/kg/day of elemental iron. Healthy term infants who are exclusively breastfed should receive 1 mg of elemental iron per kilogram per day orally starting at 4 months of age. Term infants who consume both breast milk and formula should be given 1 mg of elemental iron per kilogram per day orally starting at 4 months of age if breast milk intake comprises greater than 50% of the infant's total daily intake. For infants who are solely formula fed, iron-fortified

formulations are recommended until 12 months of age. These infants do not require additional iron supplementation. The use of cow's milk should be avoided until after 12 months of age (Reference 3). Recommended dietary intake of iron for specified age groups may be found in Table 2 (References 3, 37, 43).

Most dietary iron is available as ferric iron (Fe^{3+}). This is primarily iron that is not bound to heme. Only ferrous iron (Fe^{2+}) is absorbed in the duodenum and jejunum. Brush border ferrireductases in the GI tract reduce ferric iron to ferrous iron so that dietary iron may be absorbed (References 68, 69). Reducing substances such as ascorbic acid facilitates the conversion of ferric iron to ferrous iron, enhancing GI absorption (Reference 70). In addition, ascorbic acid is reported to have chelating properties that bind polyphenol (e.g., tannic acid) and phytates (e.g., bran, cereals), which inhibit iron absorption (Reference 71). Ingesting foods that are rich in ascorbic acid increases the absorption of non-heme iron from the diet, and its effects are more pronounced when the meal contains inhibitors of iron absorption (Reference 70).

Synthetic ascorbic acid has the same effect of improving dietary iron absorption as that found in foods (References 70, 71). For most people, taking ascorbic acid as a supplement to improve the absorption of dietary iron is unnecessary. Dietary sources of ascorbic acid are preferred. Health care professionals should advise patients and caregivers regarding RDA values if they are posed with questions about supplement use. The RDA for ascorbic acid may be found in Table 2 (References 3, 37, 43).

Diagnosis

Iron Status

Hemoglobin alone may fail to identify children at risk of developing anemia because it does not detect iron deficiency in individuals with normal-range hemoglobin values (Reference 7). Iron status tests should be used to confirm iron deficiency and guide the use of iron therapy. The iron profile typically consists of measures of serum iron concentration, total iron-binding capacity, transferrin saturation (TSAT), and serum soluble transferrin receptor. Serum iron concentration is the total amount of iron found in the serum. Total iron-binding capacity reflects the availability of iron-binding sites on transferrin. Transferrin saturation is serum iron divided by total iron-binding capacity. The value reflects the extent to which transferrin has "vacant" iron-binding sites. The *KDOQI* workgroups have defined absolute iron deficiency as a TSAT less than 20% (Reference 3). A serum soluble transferrin receptor assay measures the expression of soluble transferrin receptors. The serum soluble transferrin receptor concentration is reciprocally related to the iron supply and increases markedly in the presence of iron deficiency (Reference 72).

Ferritin

Ferritin is an indicator of iron stores status. It provides insight about whether iron stores are adequate or insufficient. Low serum ferritin is highly diagnostic for iron deficiency. In the absence of comorbidities, a ferritin value of 15 ng/mL or less indicates the absence of iron stores in children older than 6 months (References 22, 73). Individuals who have anemia from chronic disease may have normal or elevated serum ferritin, which is reflective of increased iron storage and retention in the reticuloendothelial system. Increased ferritin may also be caused by activation of the immune response (Reference 73). The lower limit for serum ferritin is defined by the KDOQI workgroup as 200 ng/mL for individuals on hemodialysis and 100 ng/mL for those with CKD not on hemodialysis (Reference 3).

Limitations to Serum Iron, TSAT, and Serum Ferritin Concentration

Serum iron, TSAT, and serum ferritin concentrations may be affected by factors unrelated to iron. Diurnal variations have been observed with serum iron and TSAT. High estrogen or progesterone states (e.g., with pregnancy, oral contraceptive use) are associated with increased TSAT values. Inflammatory states cause elevations in serum ferritin (Reference 26). Iron-deficient individuals on hemodialysis or chronically ill patients can present with high serum ferritin concentrations. The presence of malnutrition, chronic infection, or inflammation can cause serum ferritin values to be elevated (Reference 3).

Treatment

If iron supplementation is required, oral administration is the treatment of choice. Intravenously administered iron may be considered in patients who have disease states associated with malabsorption of the mineral (References 74, 75). The ferrous salt form is often used in therapy because it is most readily absorbed, although only 10% to 35% of an oral dose of ferrous sulfate is absorbed by the GI tract. The percentage of iron that is absorbed by the GI tract increases to 80% to 95% during iron deficiency (Reference 19).

Most commercially available products for oral administration are supplied as ferrous iron, and several different salt forms are on the market. Each salt form has a varying amount of elemental iron, but the extent

of iron absorption is relatively the same for all formulations. Table 4 and Table 5 provide details of elemental iron content for single-ingredient oral iron preparations and multivitamins (References 76–80).

For infants and children with mild to moderate anemia, elemental iron at a dose of 3 mg/kg given once daily or divided into two doses is recommended. Severe IDA is treated with elemental iron 4–6 mg/kg/day, usually given in three divided doses (Reference 76). Liquid oral iron preparations are preferred for infants and young children because they are unable to swallow tablets. This formulation may also be preferred for certain individuals who are unable to adequately absorb iron tablets because of poor dissolution of the film coating (Reference 81). Caution should be taken when dosing liquid iron preparations to young children because elemental iron concentrations vary among different products. Close attention should be given to interpreting the iron content because some preparations provide details in the form of milligrams of the iron salt, whereas other preparations provide iron content as milligrams of elemental iron. Several preparations provide details of iron content both as elemental iron and as the iron salt. Misinterpreting this information can lead to dosing errors. It is especially important to be aware of these issues when substituting one liquid preparation for another (see Table 4) (References 76–79).

Ideally, oral iron supplements should be taken on an empty stomach; however, this may not be possible because of the GI distress that occurs in some individuals with this therapy. Gastrointestinal distress is a common adverse effect of oral iron, and it is the most common reason for therapy nonadherence. Symptoms with a greater than 10% occurrence rate include abdominal pain, epigastric pain, nausea, vomiting, and constipation. Adequate daily fluid intake should be encouraged to alleviate constipation. Stool softeners may also be considered. Diarrhea may occur, but to a lesser extent (Reference 76–78). Administering the drug with meals may reduce GI symptoms but may decrease the extent of drug absorption. Alternatively, giving smaller doses more often may be tried. Carbonyl iron, polysaccharide iron complex, or delayed-release formulations may

Table 4. Iron Content of Select Single-Ingredient Pediatric Oral Supplements (References 76-79)

Drug	Percent Elemental Iron	Dosage Strength
Single-Ingredient Product		
Ferrous gluconate (Fergon)	11.2	240-mg tablet (elemental iron 27 mg)
Ferrous fumarate (Ferro-Sequels)	33.3	150-mg tablet (elemental iron 50 mg)
Ferrous sulfate, enteric-coated tablets	20	324-mg tablet (elemental iron 65 mg)
Ferrous sulfate, exsiccated tablets (Feosol)	32.5	200-mg tablet (elemental iron 65 mg)
Ferrous sulfate, extended-release tablets	32.1	140-mg tablet (elemental iron 45 mg)
Ferrous sulfate, slow-release tablets (Slow FE)	31.7	142-mg tablet (elemental iron 45 mg)
Ferrous sulfate, elixir	20	220 mg/5 mL (elemental iron 44 mg/5 mL)
Ferrous sulfate, liquid	20	300 mg/5 mL (elemental iron 60 mg/5 mL)
Ferrous sulfate, liquid drops (Fer-In-Sol)	20	75 mg/mL (elemental iron 15 mg/mL)
Ferrous sulfate, suspension (MyKidz Iron 10)	20	75 mg/1.5 mL (elemental iron 15 mg/1.5 mL)
Polysaccharide iron complex, capsules (various manufacturers)	100	Elemental iron 150 mg per capsule

have fewer GI effects (References 69, 74). Carbonyl iron is a pure form of iron that can be found in certain pediatric multivitamin formulations such as chewable tablets or as a gummy. This form of iron is more slowly absorbed and has a higher bioavailability than ferrous sulfate. It also has a better safety profile than ferrous sulfate. The estimated median lethal dose (LD_{50}) of ferrous sulfate is 250 mg of ferrous iron per kilogram of body weight (References 82). Toxicity studies in animals estimate the lethal dose at which no deaths occurred (LD_0) for carbonyl iron to be 10,000–15,000 mg of iron per kilogram of body weight (References 82, 83). To extrapolate these data to humans, a 10-kg child would have only consumed around one-third of the LD_0 if the child ingested 63 carbonyl iron capsules, each containing 600 mg (Reference 83). Fatal outcomes have arisen from children ingesting 30 to 40 ferrous sulfate 325 mg tablets and there have been reported deaths with very young children consuming as few as five tablets (Reference 82). Caution should still be taken with carbonyl iron because an accidental overdose can occur. Polysaccharide iron complex is available as an elixir or tablet for use in children 6 years and older (Reference 79). Enteric-coated preparations, which delay the dissolution of iron until it reaches the intestinal tract, may be considered for older children who are able to swallow tablets. Enteric-coated preparations may have lower bioavailability than film-coated preparations and oral solutions. This should be considered when changing products (Reference 84).

Table 5. Vitamin B, Folic Acid, and Elemental Iron Content of Select Multi-ingredient Pediatric Oral Supplements (Reference 80)

Drug	Percent Elemental Iron	Dosage Strength	Folic Acid	Vitamin B_{12}
Centrum Kids Complete (Carbonyl iron)	100	Elemental iron 18 mg per tablet	400 mcg per tablet	6 mcg per tablet
Flintstones Gummies Complete	-	-	100 mcg per each gummy	1.5 mcg per each gummy
Flintstones Complete Chewables (Ferrous fumarate)	100	Elemental iron 18 mg per tablet	400 mcg per tablet	6 mcg per tablet
Flintstones with Iron Chewables (Ferrous fumarate)	100	Elemental iron 15 mg per tablet	300 mcg per tablet	4.5 mcg per tablet
L'il Critters Gummy Vites	-	-	130 mcg per each gummy	3 mcg per each gummy
L'il Critters Omega-3 Gummy Fish	-	-	-	-
MyKidz Iron (with Vitamins A, C, and D)	100	Elemental iron 5 mg/mL	-	-
Nephro-Vite OTC	-	-	800 mcg per tablet	6 mcg per tablet
Nephro-Vite Rx	-	-	1000 mcg per tablet	6 mcg per tablet
One A Day Kids Scooby-Doo! Complete (Ferrous fumarate)	100	Elemental iron 18 mg per tablet	400 mcg per tablet	6 mcg per tablet
One A Day Teen Advantage for Her (Ferrous fumarate)	100	Elemental iron 18 mg per tablet	400 mcg per tablet	9 mcg per tablet
One A Day Teen Advantage for Him (Ferrous fumarate)	100	Elemental iron 9 mg per tablet	400 mcg per tablet	15 mcg per tablet
Poly-Vi-Sol	-	-	-	2 mcg/mL
Poly-Vi-Sol with Iron (Ferrous sulfate)	100	Elemental iron 10 mg/mL	-	-
Tri-Vi-Sol	-	-	-	-
Tri-Vi-Sol with Iron (Ferrous sulfate)	100	Elemental iron 10 mg/mL	-	-

Additional adverse effects associated with oral iron supplements that may be of concern to patients and caregivers are urine discoloration and dark stools. Tooth discoloration observed in individuals taking liquid iron preparations is superficial and not permanent. Diluting the oral liquid with water or juice and giving the supplement through a straw can minimize contact of the solution with teeth. Proper oral hygiene can remove and prevent tooth discoloration (Reference 76).

Monitoring

Assessing hemoglobin changes in combination with a reticulocyte count may be useful in determining treatment response to anemia because changes in the reticulocyte count can be seen in the early stages of erythropoiesis. A hemoglobin increase of 1 g/dL should occur every 2–3 weeks after therapy initiation. Some individuals may require up to 4 months of therapy for iron status to return to therapeutic range once hemoglobin has been corrected (Reference 81). Hemoglobin values that increase by more than 1 g/dL or absolute reticulocyte counts that increase by more 100,000 cells/mm^3 (100×10^6/L) after 4 weeks of therapy indicate the patient is responding to therapy (References 19, 73).

Anemia of CKD

Pathogenesis

Anemia in CKD is common and often occurs early. The cause of anemia may be erythropoietin deficiency; however, there may be other causes such as iron deficiency. Individuals on dialysis therapy have the highest risk of anemia secondary to regular blood loss to the dialysis circuit after each dialysis session. The use of anticoagulation associated with dialysis therapy increases the risk of GI bleeds, and frequent phlebotomy can contribute to blood loss and anemia.

Clinical Features and Complications

In general, complications seen in patients with CKD are similar to those in patients with IDA. Having CKD and anemia can decrease a patient's quality of life. These individuals have increased risk of target organ damage. Impaired oxygen delivery increases the workload of the heart. Over time, this could lead to ventricular hypertrophy and poor cardiac output (Reference 85).

Diagnosis

The KDOQI anemia workgroup recommends a complete blood cell count, TSAT, and serum ferritin for initial assessment of anemia in all children with a diagnosis of CKD. Hemoglobin values should be measured at least annually, and more frequent monitoring may be needed for those at higher risk of anemia. This includes children who have a greater disease burden, those who have an unstable clinical course, or those who have had a previous decrease in hemoglobin concentration. A diagnosis of anemia should be made when the observed hemoglobin value is lower than the 5th percentile of normal when adjusted for age and sex (Reference 2).

Erythropoietin Concentration

Erythropoietin is a glycosylated protein that weighs around 30,500 Da (Reference 13). The clinical utility of this laboratory test is limited. It is not routinely useful to differentiate erythropoietin deficiency from other types of anemia (Reference 2). In addition, erythropoietin levels are only useful when evaluating individuals with a hemoglobin value less than 10 g/dL. This is because erythropoietin concentrations are typically within normal range in patients having hemoglobin values higher than 10 g/dL (Reference 73).

Erythrocyte Protoporphyrin

Erythrocyte protoporphyrin (EP) is the immediate precursor of hemoglobin. It increases when insufficient iron is available for hemoglobin production. Erythrocyte protoporphyrin is more sensitive and is at least as specific for detecting IDA as hemoglobin and serum ferritin. This makes EP a useful screening tool for detecting earlier stages of iron deficiency (Reference 20). Early detection is important in children because of the developmental consequences associated with IDA. A whole-blood EP value of 35 mcg/dL or greater suggests decreased hemoglobin production and iron deficiency (References 86, 87). Erythrocyte protoporphyrin is not widely used at this time. Compared with hemoglobin, EP is a more expensive and complicated test to perform.

Reticulocyte Hemoglobin Content

Reticulocyte hemoglobin content (CHr) quantifies the amount of hemoglobin found in reticulocytes. This is another test of adequacy of iron for erythropoiesis. It is a direct measure of iron that is incorporated into newly formed RBCs. Because reticulocytes are typically 1–2 days old, this laboratory parameter reflects immediate availability of iron. Many studies have shown that CHr is effective for the early detection of iron-restricted erythropoiesis in adults who received epoetin therapy. The KDOQI recommends targeting CHr greater than 29 pg/cell as an alternative to TSAT for adult hemodialysis patients with anemia (Reference 88). Reticulocyte hemoglobin content is not widely used in children at this time, and pediatric data are limited. A study comparing the performance of laboratory parameters in 210 children (mean [SD] age, 2.7 [2.0] years) who

underwent lead screening found that CHr was the only significant predictor of iron deficiency. A CHr of 26 pg/cell or less was the optimal cutoff value for detecting iron deficiency (Reference 89).

Treatment

The goal of iron therapy is to avoid storage iron depletion, prevent iron-deficient erythropoiesis, and achieve and maintain erythropoiesis (Reference 3). For patients on hemodialysis, sufficient iron should be given to maintain a serum ferritin above 200 ng/mL and TSAT above 20%. For patients who have CKD not requiring dialysis or those who require peritoneal dialysis, serum ferritin should be maintained above 100 ng/mL and TSAT above 20% (Reference 3).

Although the absorption of oral iron may be slow, it remains an effective therapy and is preferred for children with anemia of CKD who are not on dialysis and children who are on peritoneal dialysis. The recommended dose of elemental iron is 2–3 mg/kg/day up to 6 mg/kg/day (maximum 150–300 mg of elemental iron per day) given in two or three divided doses. To optimize GI absorption, doses of oral iron preparations should be taken at least 2 hours before or 1 hour after ingesting any calcium-containing phosphate binders (Reference 2). There are several reasons why an individual may not respond to oral iron supplementation. Therapy nonadherence, impaired GI absorption of iron, inflammation, and chronic bleeding can all contribute to therapy unresponsiveness. Most data supporting the use of intravenous iron are found in the dialysis patient population. Red blood cell transfusions are necessary if patients are symptomatic after experiencing acute bleeding, acute hemolysis, or blood loss from surgery (Reference 3).

Intravenous Iron

Injectable iron therapy is generally reserved for when oral therapy has failed. However, it is the preferred route of administration for treating anemia in children on hemodialysis therapy. Current intravenous iron preparations consist of iron complexed to a carbohydrate moiety. In the body, the reticuloendothelial cells separate the iron from the iron-carbohydrate complex (Reference 90). The iron is then available for binding to transferrin for transport throughout the body. It may be incorporated into the body's total iron stores, or it may be used for hemoglobin synthesis (Reference 90).

No adequately powered studies exist that directly compare efficacy between parenteral iron preparations. Hypersensitivity reactions can occur with all injectable iron preparations; however, they are more pronounced with iron dextran. Iron toxicity can be detrimental in both acute and chronic situations. Care should be taken to monitor for iron overload in patients with predisposing conditions.

Iron Dextran

Iron dextran is an older formulation of parenteral iron. It is ferric hydroxide complexed with polymerized dextran. In comparative studies, iron dextran showed higher rates of adverse events than newer parenteral iron preparations. Use of this iron preparation is associated with increased risk of hypersensitivity reactions. Iron dextran should generally not be given to infants in the first 4 months of life. Before iron dextran is administered, all patients should receive an intravenous test dose of 0.5 mL (25 mg) (Reference 91). Cases have been documented in which patients tolerated a test dose but then experienced a hypersensitivity reaction with treatment doses. Caution should be taken to maintain an administration rate below 50 mg/minute when giving treatment doses. The dosage calculation for intravenous infusion in an iron-deficient patient is described below (Reference 91).

Calculation of iron dextran dose for children 5–15 kg is as follows (Reference 91):

$$\text{dose (mL)} = 0.0442\ [\text{desired hemoglobin (g/dL)} - \text{observed hemoglobin (g/dL)}] \times W + (0.26 \times W)$$

where W = weight in kg.

$$\text{weight in kg} = \frac{\text{weight (lb)}}{2.2}$$

Iron Sucrose (Iron Saccharate)

Iron sucrose is an aqueous complex of iron hydroxide in sucrose. It can be given undiluted by slow intravenous push or as an intravenous infusion. Iron sucrose is not FDA approved for use in children; however, it is prescribed. The pediatric dose for correcting iron status in hemodialysis-dependent patients is 1 mg/kg/dose per dialysis session. The maximum single dose is 100 mg. The suggested maintenance dose is 0.3 mg/kg/dose given at each dialysis session (Reference 92). Iron sucrose has been successfully administered to adult patients with sensitivity to iron dextran and does not require a test dose before administration (References 2, 93). Safety data related to the use of iron sucrose in children are limited. A retrospective study involving eight individuals who received at least one dose of iron sucrose reported no serious adverse events (Reference 2).

Ferric Gluconate

Ferric gluconate is a sodium ferric gluconate complex in sucrose. Ferric gluconate is FDA approved for use in children 6 years and older undergoing hemodialysis and receiving epoetin therapy (Reference 94). The recommended pediatric regimen is 1.5 mg/kg/dose of elemental iron at each dialysis session for eight doses total. The maximum single dose is 125 mg. A slow infusion rate is recommended over 60 minutes (Reference 94). Hypersensitivity reactions are rare (Reference 93). In a trial involving children who received eight intravenous doses of ferric gluconate, no child developed an allergic or anaphylactic reaction during the immediate treatment. One child who was given a 1.5-mg/kg dose developed an isolated episode of mild nausea, vomiting, and diarrhea (Reference 2).

Ferumoxytol

Ferumoxytol is the newest parenteral iron preparation on the market. It is a superparamagnetic iron oxide coated with a low-molecular-weight semisynthetic carbohydrate. The safety and efficacy of ferumoxytol use in children have not been established (Reference 95).

Recombinant Human Epoetin

Epoetin is often used to stimulate erythropoiesis in patients with renal dysfunction. Most of the available data for use in children involve short-acting agents such as epoetin alfa (Reference 3). Because of convenience, subcutaneous administration is favored. Observational trials of children suggest that administering short-acting epoetin subcutaneously is more efficacious than using the intravenous route (Reference 3).

Information derived from registry data suggests that a higher starting dose of a short-acting epoetin is required for hemodialysis patients, compared with peritoneal dialysis patients, to achieve target hemoglobin values of 11–12 g/dL. The mean dose of short-acting epoetin for children on hemodialysis is 300 units/kg/week compared with 225 units/kg/week for peritoneal dialysis patients. Young children require higher doses per kilogram of body weight than older children. Infants on average require 350 units/kg/week. Those between 2 and 5 years of age and 6 and 12 years of age require slightly lower doses (about 275 units/kg/week and 250 units/kg/week, respectively). Children older than 12 years need around 200 units/kg/week (Reference 3).

Pediatric studies involving long-acting epoetin (darbepoetin alfa) are limited. One small study involving children on hemodialysis therapy proposed a dose conversion of 0.5 mcg of darbepoetin alfa for every 200 units of erythropoietin alfa (Reference 3).

In children with CKD who are not receiving dialysis, the mean dose of short-acting erythropoietin alfa required to maintain target hemoglobin values between 11.5 g/dL and 13.5 g/dL is 133 units/kg/week. The dose range is 75–300 units/kg/week. Darbepoetin alfa at a dose of 0.45 mcg/kg/week showed similar efficacy (Reference 3).

Up to 10% of patients with CKD have a poor response to epoetin therapy. Hyporesponsiveness to epoetin therapy is defined as persistently low hemoglobin (less than 10 g/dL), despite treatment with clinically appropriate doses (Reference 3). Clinicians should rule out nonadherence and verify that the patient has sufficient iron available for erythropoiesis. Transferrin saturation percent should be greater than 20%, and serum ferritin should be higher than 100 ng/mL. Other potential causes of hyporesponsiveness include infection, inflammation, and inefficient dialysis. It is believed that uremia is associated with increased release of proinflammatory cytokines in the bone marrow. Chronic inflammation can lead to impaired erythropoiesis (Reference 96).

Blood pressure should be assessed because hypertension in children receiving epoetin is an important concern. One pediatric study involving children 4 months to 21 years of age who received low or high doses of epoetin found that epoetin treatment was associated with a significant increase in diastolic blood pressure compared with baseline. Thrombotic events have also been reported in children receiving epoetin (Reference 2).

Monitoring

An increase in the reticulocyte count is not observed for at least 4–7 days after starting therapy. A decision about the effectiveness of treatment should not be made for 3–4 weeks after treatment initiation (References 20, 81). Erythropoietic response to iron replacement is considered appropriate if the hemoglobin concentration increases by at least 2 g/dL or reaches normal values within 4 weeks of treatment. The 2 g/dL increase can be reached by intravenous iron therapy within 2–4 weeks (Reference 3). The hemoglobin target for all children with anemia of CKD is 11–12 g/dL (References 2, 88). The monitoring interval is extended to every 1–3 months once the patient has achieved a stable iron dose. More frequent monitoring is required for individuals who have experienced recent bleeding, for postsurgical or hospitalized patients, or for those who are hyporesponsive to epoetin (Reference 3). Erythropoietin concentrations have also been used to evaluate a patient's responsiveness to epoetin therapy (Reference 73).

Monitoring intervals are the same for individuals who receive oral iron, intravenous iron, or intravenous iron with epoetin. Recommendations for epoetin dose increases and decreases vary among different expert panels. According to the European Paediatric

Peritoneal Dialysis Working Group, a minimally acceptable increase in hemoglobin value is 0.66 g/dL per month. Other panels such as KDOQI recommend hemoglobin increases between 1 g/dL and 2 g/dL per month. Epoetin dosage adjustments should be considered for children who have a greater than 0.5 g/dL increase per week in hemoglobin to avoid exceeding the target value (Reference 2). It is also recommended to decrease the epoetin dose rather than hold or discontinue the medication when hemoglobin is above target range (References 2, 3). The ideal approach to therapy is to decrease the dose if hemoglobin is elevated (References 2, 3, 88).

Iron status tests should be performed monthly during initial treatment with epoetin. Serum ferritin should be maintained above 100 ng/mL, and TSAT should be above 20% during epoetin treatment. The monitoring interval for assessing iron status may be extended to every 3 months for children who are on a stable epoetin dose or for those who are on hemodialysis and are not receiving epoetin therapy (Reference 2).

Conclusions

Anemia is commonly caused by iron, folate, and/or vitamin B_{12} nutritional deficiencies. Severe inflammation, CKD, or other chronic illnesses can also cause anemia. Rapid growth and development, together with decreased stores of certain nutrients compared with adults, contribute to increased risk of anemia in children.

Mild cases of anemia can still have effects on oxygen transport capacity of the blood and may produce symptoms such as irritability, lethargy, and decreased physical endurance. Additional symptoms vary and pertain to the cause of anemia. For example, folate deficiency in pregnant women can lead to neural tube defects in the fetus, vitamin B_{12} deficiency is associated with neurologic damage, and iron deficiency is associated with poor cognitive and motor development.

Early detection of deficiency and prevention of anemia are essential. In the United States, fortifying foods is one measure taken to prevent nutritional deficiencies. Many laboratory assays are available; however, hemoglobin is currently the standard laboratory assessment for detecting and monitoring anemia.

Pediatric cases of folate and/or vitamin B_{12} anemia in the United States are rare. If treatment is required, folic acid is available in oral and injectable dosage forms. The dosing strategy is the same for all formulations. Vitamin B_{12} deficiency may be treated with cyanocobalamin given intramuscularly or subcutaneously. Individuals with severe vitamin B_{12} deficiency could develop profound and potentially fatal hypokalemia. It is important to closely monitor patients during the first 48 hours after initiating therapy, and potassium replacement should be available for use if the need arises.

Iron deficiency is the most common form of nutritional deficiency worldwide. In the United States, the prevalence of iron deficiency among young children is of concern. The AAP has published guidelines detailing measures that should be taken to detect and prevent IDA in infants and young children. Oral iron is the therapy of choice for treating iron deficiency and IDA. Gastrointestinal adverse effects from oral therapy can contribute to nonadherence. Giving iron in smaller doses or with food can help alleviate GI effects.

Anemia of CKD may be caused by IDA in combination with erythropoietin deficiency. This type of anemia can occur early in CKD, and it can decrease a child's quality of life. Long-standing anemia can lead to ventricular hypertrophy and cardiac dysfunction. Oral iron is the therapy of choice; however, intravenous iron may be necessary. Children with malabsorptive disorders may benefit from intravenous iron, and those receiving dialysis often require intravenous iron therapy. If intravenous iron is needed, newer formulations (e.g., ferric gluconate and iron saccharate) are preferred because of their better adverse effect profile compared with iron dextran. Epoetin is also commonly used to treat anemia of CKD. Most data for use in children involve the short-acting formulation, epoetin alfa. Children who require epoetin should have a baseline iron profile to ensure adequate iron status before starting epoetin. Hemoglobin, while on epoetin therapy, should not exceed 13 g/dL.

Although untreated anemia of all types may result in considerable organ dysfunction, it is reassuring that early detection and treatment can prevent these complications. Preventive medicine, instead of reactive medicine, should be the gold standard.

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CHAPTER 48

ANTICOAGULATION

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LEARNING OBJECTIVES

1. Understand the epidemiology and pathophysiology of pediatric thrombosis, including common risk factors for thrombosis.
2. Understand the pharmacology and therapeutics of antithrombotic agents including unfractionated heparin, warfarin, low-molecular-weight heparin, and direct thrombin inhibitors.
3. Know how to monitor pediatric patients receiving anticoagulant medications for the treatment and prevention of thrombosis.

ABBREVIATIONS IN THIS CHAPTER

ACT	Activated clotting time
Anti-Xa	Antifactor Xa
aPTT	Activated partial thromboplastin time
DVT	Deep venous thrombosis
HIT	Heparin-induced thrombocytopenia
INR	International normalized ratio
PE	Pulmonary embolism
UFH	Unfractionated heparin

INTRODUCTION

This chapter will review the epidemiology and etiology of thrombosis in the pediatric population and will focus on the pharmacologic treatment and prophylaxis of thrombosis in pediatric patients. Because anticoagulant agents are used in a wide variety of practice settings, this chapter must be limited to indications that are common to pediatric patients, but also outside the purview of other disease states that are covered in separate chapters of this book (e.g., prophylaxis of thrombosis in patients with cancer or heart disease). Other patient populations that receive anticoagulants, but that will not be covered in this chapter, include patients undergoing hemodialysis, patients in the cardiac catheterization laboratory, and patients in the operating room (including those undergoing cardiopulmonary bypass). Primarily, this chapter will focus on thromboses that occur within the vasculature (deep venous thrombosis [DVT], arterial thrombosis, pulmonary embolism [PE], ischemic stroke) and intravascular catheter patency in the pediatric population. The intention is that a review of these areas, with a focus on the available pharmacotherapy data for them, will cover most pediatric pharmacist-patient interactions.

DEEP VENOUS THROMBOSIS

The epidemiology of pediatric DVT is markedly different from that of adult DVT. Most adult DVTs occur in the lower extremities, whereas pediatric DVTs often occur in both the upper and lower extremities. Unlike in adults, the etiology of pediatric DVT is rarely idiopathic because pediatric patients have a lower thrombotic potential compared with adults owing to their decreased concentrations of plasma procoagulant factors, decreased thrombotic potential of the vascular endothelium, and increased inhibition of thrombin by alpha-2 macroglobulin (References 1, 2).

The incidence of pediatric DVT has been increasing. In 2000, an incidence of 5.3 per 10,000 pediatric hospital admissions was noted, which has subsequently increased to a current incidence as high as 58 per 10,000 pediatric hospital admissions (References 1–4). In general, infants and adolescents have the highest incidence of DVT (Reference 4). Central venous catheters are the primary underlying factor for developing a DVT, particularly in younger and critically ill children, and account for most DVTs in the upper parts of the vasculature. Other factors include sepsis, nephrotic syndrome, malignancy, surgery, congenital heart disease (with or without prosthetic materials), antiphospholipid antibody syndrome, L-asparaginase therapy, and congenital or acquired prothrombotic conditions. Adolescent females also have a higher risk of developing a DVT, presumably because of oral contraceptive use (References 1–5).

Many pediatric patients with a DVT are asymptomatic (References 2, 6). Patients with symptoms note pain, discoloration, and swelling in the area distal to the DVT. Catheter-related DVTs are often initially noticed when the catheter begins to malfunction or when the thrombus becomes infected and no other source for infection in a patient can be found (References 1, 2, 6). Neonates may present with thrombocytopenia caused by thrombus consumption of platelets. D-dimer tests can be used to assist in the detection of a DVT, and Doppler ultrasonography is used often for detecting

extrathoracic DVTs. Echocardiography can be useful for identifying a thrombus within the vena cavae, and a computed tomography (CT) scan is often used for detecting a thrombus within the abdominal and pelvic regions (References 1, 2, 6).

Mortality rates for venous thromboembolism have been previously reported at 1% to 2%, but recently, they have been noted to be as high as 8% for a patient admitted with a DVT (References 2, 3, 6). Recurrence rates after resolution of initial DVT are high (9% to 21%), most likely because of underlying chronic conditions (Reference 5). Postthrombotic syndrome can occur in pediatric patients after resolution of a DVT in the leg; it consists of pain, swelling, altered skin pigmentation, and skin ulceration near the site of the DVT. The etiology of this condition is unclear, but symptoms are usually mild in children (References 2, 7).

Long-term anticoagulation is the primary therapy for treatment of pediatric DVT. For an outpatient with an uncomplicated DVT, use of enoxaparin or warfarin is typically indicated for 3–6 months (Reference 8). Laboratory monitoring (anti-Xa or INR) should occur at the beginning of therapy and regularly throughout therapy, especially in younger patients, to ensure the attainment of therapeutic concentrations. In particular, warfarin can be difficult to manage in infants and children (Reference 9). Patients with a large thrombus, evidence of progression of thrombus while on anticoagulant therapy, or a thrombus that completely occludes a vessel may require more than 6 months of therapy. Inpatients or critically ill patients with a DVT may be placed on unfractionated heparin (UFH) titrated to therapeutic aPTT or anti-Xa concentrations before the transition to enoxaparin or warfarin as the patient stabilizes. The choice of initial anticoagulant therapy can vary on the basis of patient characteristics and pathophysiology.

Pulmonary Embolism

Pulmonary embolism is a rare event in pediatric patients, with reported rates at less than 1 per 100,000 children per year (References 10, 11). However, this is likely an underestimation of the true incidence because most patients with a PE are asymptomatic unless the embolus is very large (Reference 12). In pediatric populations with risk factors, the percentage of patients who were asymptomatic but had PEs was as high as 50% (Reference 13). Risk factors for PE are similar to those for DVT, and the incidence of PE is likely increasing because of the increased use of central venous catheters (Reference 3).

As previously stated, most pediatric patients who present with a PE will be asymptomatic unless the PE is large (obstructing more than 50% of the pulmonary circulation). However, patients with preexisting hemodynamic instability or decreased pulmonary blood flow may have symptoms even with small emboli. Primary symptoms include dyspnea, cough, hemoptysis, and chest pain (Reference 12). Patients may also have a concurrent DVT at another location in the body. Increased pulmonary vascular resistance caused by an embolus may lead to elevated right ventricular pressures or tricuspid regurgitation. Ventilation and perfusion mismatch may occur, and patient arterial oxygen saturation may decrease. Ventilated patients may have a sudden increase in oxygen requirements. Arrhythmias and even sudden death have occurred in pediatric patients with a PE. A D-dimer test can be useful for determining an embolus. Diagnosis can be made by the use of noninvasive imaging, such as magnetic resonance imaging (MRI), CT scan, ventilation perfusion lung scanning, or pulmonary angiography. However, the data for use of these modalities are primarily extrapolated from adult experience (Reference 12).

The goal of therapy is to eradicate the PE and prevent the recurrence or propagation of the embolus. Nonpharmacologic therapies for PE include surgical embolectomy and interventional procedures. Surgical procedures can have substantial associated morbidity (Reference 14). Catheter-based techniques can minimize morbidity, but they should only be performed by clinicians with experience and in centers that can offer this therapy (Reference 15).

Choice of pharmacologic therapy for PE will be based on the acuity of the patient and the size of the embolus. Unfractionated heparin is often the first-line agent for acute treatment of PE in children. If a patient is experiencing hemodynamic compromise, the use of alteplase for thrombolysis is an option, but definitive recommendations for the use of alteplase in pediatric patients are unavailable because of the small number of patient cases that have been reported (References 16–20). Use of alteplase for PE in a pediatric patient should be evaluated on a case-by-case basis because morbidity from hemorrhage can be high. For longer-term therapy, enoxaparin or warfarin can be used, depending on patient factors and preferences. Patients will often be treated for at least 6 months after receiving a diagnosis of a PE, but the optimal treatment duration in pediatric patients is currently unknown (Reference 8).

Arterial Thrombosis

Arterial thrombosis is a rare but potentially devastating condition. Primarily, the thrombosis occurs because of indwelling arterial catheters or after cardiac catheterization at the arterial access point of catheter insertion (References 21, 22). Damage to the endothelium of the artery, resulting in inflammation and clotting cascade activation, is the primary pathophysiology for arterial

thrombosis (Reference 8). Younger patients who have had arterial catheters indwelling for extended periods are at the greatest risk of arterial thrombosis (Reference 23). In addition, if the patient did not have a prophylactic infusion of UFH through the arterial catheter, he or she is at increased risk of thrombosis. Septic patients or patients with underlying coagulopathies with indwelling catheters are also at increased risk of arterial thrombosis (References 8, 22, 24, 25).

Patients with an arterial thrombosis will typically present with an acute loss of circulation to the affected limb or region. Doppler ultrasonography for detection of pulses distal to the thrombus can be useful to assess the clinical severity of the thrombus. Contrast angiography is the gold standard for assessing arterial thrombosis, but it is difficult to perform in young children (Reference 26).

If possible, the first step for treatment of arterial thrombosis is to remove the offending catheter. Nonpharmacologic treatment of arterial thrombosis is typically reserved for life- or limb-threatening conditions. Thrombectomy, either surgically or interventionally can be performed for large thrombi. Devices to mechanically destroy a thrombus have also been used. However, these devices have the disadvantage of potentially causing trauma to the vessel wall and are sometimes unable to extract free-floating thrombus (Reference 27).

Pharmacologic therapy is instituted on the basis of the severity of arterial blockage. Unfractionated heparin or enoxaparin is typically a first-line agent for arterial thrombus that is not immediately life or limb threatening (References 26, 28). Alteplase has been used in emergency cases for the dissolution of an arterial thrombus (Reference 29). The use of alteplase has a high bleeding risk, and caution should be exercised in patients with the potential for hemorrhage, such as premature infants, patients who have undergone recent major surgery, or patients with baseline bleeding disorders (Reference 8).

Ischemic Stroke

Acute ischemic stroke is uncommon in infants and children, with an incidence ranging from 2 to 8 per 100,000 children per year in the United States. Morbidity is very high in patients who have had an ischemic stroke, with as many as 70% of patients having a persistent neurologic deficit. Risk factors for ischemic stroke include cardiovascular disease (congenital or acquired), vasculopathies, sickle cell disease, and other coagulopathies (References 30, 31). However, about 30% of the children presenting with an ischemic stroke have no identifiable risk factors (References 32, 33).

Pediatric patients with an ischemic stroke will present with monoparesis or hemiparesis, vision changes, numbness, ataxia, headache, seizures, and/or altered mental status. These signs and symptoms will vary depending on the age of the child and any other comorbid conditions that are present (References 30–34).

Initial medical management of the pediatric patient with ischemic stroke includes maintaining airway, breathing, and circulation and performing hematologic studies to evaluate for baseline coagulopathies. Use of brain CT or MRI can be useful to identify whether the stroke is ischemic or hemorrhagic, but the choice of modality must be evaluated on a case-by-case basis (Reference 35). Monitoring of blood pressure and maintenance of blood glucose are also important parameters to evaluate because patients with ischemic stroke may have worse outcomes with hypotension or hyperglycemia (References 36, 37). Surgical or interventional procedures may be an option, but there are limited data to routinely recommend their use in pediatric patients. Dysregulation of body temperature has been noted, and acetaminophen should be used to decrease temperature in patients with fever (References 36, 37). Seizures are common in patients with ischemic stroke; fosphenytoin and levetiracetam have both been used in this subset of patients (Reference 37).

Anticoagulation therapy for pediatric patients can be quite varied, and no current standard for treatment of ischemic stroke exists. A recent survey of centers that care for patients with acute ischemic stroke showed almost equal use of antiplatelet therapy and anticoagulation in pediatric patients with acute ischemic stroke, with a smaller percentage using both (Reference 36). Unfractionated heparin or enoxaparin has traditionally been a first-line treatment option, with enoxaparin more traditionally used in the post-acute stroke period (Reference 38). Warfarin can be used as long-term therapy for stroke after the acute period. Antiplatelet therapy for acute ischemic stroke can also be quite varied, but traditionally, it has consisted of aspirin in the acute and chronic periods. In addition, clopidogrel and dipyridamole can be used, but limited data are associated with the use of either of these agents in the acute or chronic period in pediatric patients (References 39, 40). Duration and intensity of chronic therapy will largely depend on the etiology for the stroke and any underlying comorbidities that place the patient at increased risk of future events.

Maintenance of Arterial or Venous Catheter Patency

The previous section of this chapter focused on the treatment of thromboembolism within the various vascular structures of the body. As previously mentioned, the main cause of thromboembolism in pediatric patients is the presence of an indwelling venous or arterial catheter. To prevent thromboembolism and maintain these catheters in working order, prophylaxis is often necessary. For patients who have developed a thrombus at the tip of a catheter, treatment may be necessary to prevent the removal or replacement of the catheter.

In the hospital setting, several different techniques have been employed to prevent catheter-related thrombosis. Because of the wide variety of patients, UFH concentrations, use of bolus or continuous-infusion regimens, and catheter size and type, definitive recommendations for prophylaxis are currently unavailable. The use of UFH is not inconsequential because adverse events can occur even with the routine flushing of catheters (References 41–44). Using UFH as a bolus to flush central venous catheters has been shown to decrease the incidence of patient thromboembolism and the incidence of catheter replacement in pediatric patients compared with normal saline flushes. However, other studies have shown that low-dose UFH as a continuous infusion or bolus does not increase the time of patency compared with normal saline for central venous catheters in neonates (References 45–47). Other methods of preventing catheter-related thrombosis have also had unclear results. Routine low-dose anticoagulation of critically ill pediatric patients (not directed through the catheter) has not shown a benefit (Reference 41). A recent Cochrane Review suggests that using a low concentration of UFH as a continuous infusion through a central venous catheter in neonates prevents thrombosis (Reference 48). Reports of using heparin-bonded catheters have shown promise in preventing thromboembolism in pediatric patients, but this reduction may be the result of prevention of infection, not a direct anticoagulant effect (References 49–54). In the outpatient setting, prevention of catheter-related thrombosis has been evaluated in patients receiving warfarin and long-term total parenteral nutrition (Reference 55). Reviews of the literature have shown that more powerful study designs are necessary to obtain a definitive answer for the optimal regimen for prophylaxis of arterial and venous catheters (References 56–58).

Alteplase has been the most frequently studied agent for the treatment of catheter occlusions in pediatric patients, with many reports showing safety and efficacy in clearing catheter occlusions (References 59–66). In addition, interventional catheter-directed thrombolytic therapy with alteplase has been shown to be successful in clearing catheter occlusions compared with direct instillation of alteplase into the affected catheter (References 67, 68).

Pharmacology

Aspirin

Aspirin mediates antiplatelet effects by irreversibly acetylating cyclooxygenase-1, thereby decreasing the amount of thromboxane A2 generated. A decrease in thromboxane A2 leads to decreased platelet aggregation (References 69, 70). Absorption is primarily in the stomach and small intestines, with greater absorption in the small intestines for enteric-coated formulations (Reference 69). Peak serum concentrations for non–enteric-coated or non–delayed-release aspirin formulations occur about 1–2 hours after oral ingestion. Aspirin is primarily hepatically metabolized and renally eliminated as unchanged drug or as metabolites and is dialyzable (Reference 69). Aspirin dosing in pediatric patients, which is not well defined, is often rounded to the nearest ¼ tablet due to unavailability of a commercially produced suspension (Table 1).

Adverse events with aspirin include bleeding caused by the lack of platelet aggregation, and enteric-coated formulations have been developed primarily to avoid gastrointestinal bleeding (Reference 69). Reye syndrome, a form of noninflammatory hepatic encephalopathy, has been linked to aspirin therapy in patients with viral illness. Historically, patients younger than 18 years have been advised not to take salicylate-containing products if they have a viral illness, to avoid the development of Reye syndrome (Reference 71). However, data supporting the link between aspirin use, viral illness, and Reye syndrome are weak, and the true etiology of Reye syndrome likely has a strong genetic component and is multifactorial (Reference 71).

Dipyridamole

Dipyridamole inhibits platelet aggregation by decreasing phosphodiesterase, which results in an increase in cyclic adenosine monophosphate (cAMP). This increase in cAMP decreases platelet aggregation and may cause mild vasodilation. Prostacyclin release may also be induced by dipyridamole, which can also decrease platelet aggregation and cause arterial vasodilation (References 69, 72). Few data are available regarding the pharmacokinetics of dipyridamole in pediatric patients, and most dosing has been extrapolated from adult data (References 73–76) (Table 1). Dipyridamole is primarily hepatically metabolized and, when administered enterally, has slow and variable absorption from the gut.

Adverse events with dipyridamole include bleeding, caused by antiplatelet effects, and events related to vasodilation, such as syncope, dizziness, and hypotension. Bleeding risk may increase with the concomitant use of other antiplatelet or anticoagulant agents (References 69, 72). Data are limited for an accurate portrayal of the adverse events of dipyridamole in the pediatric population, and patients should be monitored closely for adverse events.

Clopidogrel

Use of clopidogrel in the pediatric population is a relatively new phenomenon. However, more pediatric patients are being prescribed clopidogrel for a wide variety of indications, and dosing methods are being refined

Table 1. Dosing and Monitoring of Commonly Used Anticoagulant and Antiplatelet Agents in Pediatric Patients (References 69, 72)

Medication	Dosing and Administration	Suggested Monitoring Parameters
Abciximab (ReoPro)	Infants, children, adolescents: Treatment: Bolus IV: 0.25 mg/kg/dose Continuous IV infusion: 0.125 mcg/kg/minute	aPTT; PT; fibrinogen; platelet count; bleeding
Alteplase (Activase, Cathflo)	Infants, children, adolescents: Treatment of systemic thrombus: Continuous IV infusion: 0.1–0.6 mg/kg/hour for 6 hours Note: UFH infusion is typically continued during alteplase infusion to prevent rethrombosis. Treatment of catheter thrombus: (low dose) Continuous IV infusion: 0.01–0.05 mg/kg/hour Catheter clearance: Dose: 0.5–2 mg in 1–3 mL of normal saline instilled into the catheter and aspirated after a 1- to 2-hour dwell time. Do not infuse into patient.	aPTT; anti-Xa; plasminogen; fibrinogen; bleeding
Argatroban	Infants, children, adolescents: Treatment: Continuous IV infusion: 1.75 mcg/kg/hour Dose may need to be reduced in patients with hepatic dysfunction.	aPTT; platelet count; bleeding; serum creatinine; liver function
Aspirin	Prophylaxis: Infants, children, adolescents: Oral: 1–5 mg/kg/day once daily; maximum 81 mg/day Kawasaki disease: Infants, children, adolescents: Oral: 80–100 mg/kg/day divided four times/day for 14 days, or until defervescence. Then 3–5 mg/kg/day once daily	Platelet count; bleeding
Bivalirudin (Angiomax)	Infants, children, adolescents: Treatment: Bolus IV: 0.75 mg/kg/dose Continuous IV infusion: 1.75 mg/kg/hour	aPTT; ACT; platelet count; serum creatinine; bleeding
Clopidogrel (Plavix)	Treatment, prophylaxis: Infants ≤ 24 months: Oral: 0.2 mg/kg/dose once daily Children > 2 years: Oral: 1 mg/kg/dose once daily; maximum 75 mg once daily	Platelet count; bleeding
Dipyridamole (Persantine)	Treatment, prophylaxis: Infants, children, adolescents: Oral: 3–6 mg/kg/day divided three times day; maximum: 400 mg/day	Platelet count; bleeding
Enoxaparin (Lovenox)	Treatment: subcutaneous: Preterm neonates: 2 mg/kg/dose twice daily Term neonates: 1.7 mg/kg/dose twice daily Infants 1 to < 2 months: 1.5 mg/kg/dose twice daily Children > 2 months: 1 mg/kg/dose twice daily Adolescents and adults: 1 mg/kg/dose twice daily Prophylaxis: subcutaneous: Neonates, infants, and children: 0.75 mg/kg/dose twice daily Adolescents and adults: 0.5 mg/kg/dose twice daily	Anti-Xa; platelet count; serum creatinine; bleeding Goal anti-Xa concentrations for treatment of thrombus are typically 0.5–1 unit/mL and should be drawn 4–6 hours after a dose.

(continued)

Table 1. Dosing and Monitoring of Commonly Used Anticoagulant and Antiplatelet Agents in Pediatric Patients (References 69, 72) *(continued)*

Medication	Dosing and Administration	Suggested Monitoring Parameters
	Prophylaxis for adolescents and adults may be a standard dose (40 mg subcutaneously) and can depend on indication for prophylaxis. Injection sites should be rotated (abdomen, thigh, upper arm) to prevent injection site bruising and lipomas.	
Unfractionated heparin	Treatment of venous or arterial thrombus: Infants ≤ 1 year starting dose: Bolus IV: 75 units/kg/dose Continuous-infusion IV: 28 units/kg/hour Children > 1 year starting dose: Bolus IV: 75 units/kg/dose Continuous IV infusion: 20 units/kg/hour Adolescents and adults, starting dose: Bolus IV: 80 units/kg/dose (maximum 5000 units) Continuous IV infusion: 18 units/kg/hour Maintenance of catheter patency: Arterial: neonates: 5 units/mL infused at 1 mL/hour Infants and children: 1 unit/mL infused at 1 mL/hour Venous: Neonates: 10 units/mL as a bolus flush Infants and children: 10–100 units/mL as a bolus flush	aPTT; anti-Xa; platelet count; bleeding; thrombosis; serum creatinine Infusions should be titrated to a therapeutic aPTT or anti-Xa values, which may be institution-specific. aPTT values are typically calibrated to achieve an anti-Xa concentration of 0.35–0.7 unit/mL. UFH use to maintain catheter patency will vary on the basis of patient- and institution-related factors. Caution should be warranted to ensure that young patients do not receive therapeutic doses of UFH from several flushes or infusions.
Warfarin (Coumadin)	Treatment, prophylaxis: Infants, children, adolescents: Starting dose: oral: 0.2 mg/kg/dose; maximum 5 mg/day Note: Loading doses of > 5 mg are generally not recommended. Patients with drug interactions, Fontan, or hepatic disease: Starting dose: oral: 0.1 mg/kg/dose Usual therapeutic doses: Infants < 1 year: 0.34 mg/kg/day Children 1–12 years: 0.15–0.19 mg/kg/day Adolescents: 0.14 mg/kg/day	PT; INR; bleeding; thrombosis; dietary intake of vitamin K; drug-drug interactions Dose should be titrated to goal INR value for the patient.

ACT = activated clotting time; anti-Xa = antifactor Xa; aPTT = activated partial prothrombin time; INR = international normalized ratio; IV = intravenous; PT = prothrombin time; UFH = unfractionated heparin.

(References 77, 78) (Table 1). A formulation for a suspension of clopidogrel has recently been published that will allow greater ease of administration to younger patients (Reference 79). Clopidogrel is extensively hepatically metabolized into an active thiol compound, which irreversibly binds to the P2Y12 platelet receptors and prevents activation of the glycoprotein IIb/IIIa platelet-binding complex. The metabolism of clopidogrel involves cytochrome P450 (CYP) enzymes, particularly CYP 2C19 and 3A4. Therefore, not all patients who receive clopidogrel will have the same degree of platelet inhibition because of the variability in patient enzyme expression and the subsequent variation in the transformation of clopidogrel into an active form (Reference 80). Clinically, the implications of patient pharmacogenomic variability and therapeutic outcomes with clopidogrel are unknown. In addition, drug interactions play a role in the efficacy of clopidogrel platelet inhibition. Concomitant use of proton pump inhibitors with clopidogrel has been identified as a potentially significant drug interaction in both adults and children (References 81, 82). The exact clinical implications of this interaction have not yet been elucidated. Practitioners should be aware of the potential for significant drug interactions with clopidogrel and other medications that are metabolized or are substrates for the CYP family of enzymes.

Warfarin

Warfarin has been widely used in both adult and pediatric patients for many years. The reader is encouraged to review current guidelines for warfarin therapy in the latest *CHEST* supplement (Reference 8).

Anticoagulation is achieved by inhibition of vitamin K epoxide reductase, which is responsible for converting the vitamin K–dependent clotting factors (II, VII, IX, X) to active forms. Warfarin also inhibits the anticoagulant proteins C and S.

Warfarin dosing in pediatric patients is on a milligram per kilogram basis, with reductions in dose for drug interactions or disease states (Reference 9) (Table 1). Because of the varying half-lives of the vitamin K–dependent clotting factors, the full effect of warfarin will typically not be seen until after 5–7 days of therapy. Dosing algorithms or guidelines and, more recently, pharmacogenomic testing can assist with identifying appropriate warfarin doses for therapeutic effect (References 83, 84). Therapy with warfarin in pediatric patients has been traditionally difficult to manage. The international normalized ratio (INR) is used to monitor warfarin therapy, but most pediatric goal INR ranges have been extrapolated from adult data. Variation in INR values is high in pediatric patients, and close monitoring is warranted (References 9, 85–88). Age, concomitant medications, disease state, nutritional status, and pharmacogenetic profiles of patients have been shown to alter dosing regimens of warfarin in pediatric patients (References 9, 89–91). Younger patients often require higher warfarin doses per kilogram of body weight to achieve therapeutic INR values (References 9, 89–91) (Table 1). The effect of vitamin K supplementation in diets as well as enteral feeding formulas or breastfeeding should be considered when evaluating warfarin therapy in pediatric patients (Reference 9).

Significant morbidity associated with warfarin therapy has driven the development of methods to improve warfarin dosing and monitoring. The use of standardized guidelines, health care provider and family education programs, computerized algorithms, and home INR monitoring are examples of interventions used to improve warfarin dosing and monitoring (References 84, 86, 92–100). Drug interactions play a role in the morbidity of patients taking warfarin, and pediatric patients likely have an exposure to interacting medications that is different from adult patients receiving warfarin (References 101, 102). Overall, a multidisciplinary approach to the management of warfarin therapy, with close monitoring, is ideal to maximize efficacy and minimize patient morbidity.

Pharmacogenomic testing has recently come to the forefront as a method for improving warfarin dosing and identifying patients at risk of warfarin-related morbidity (References 83, 103–106). Polymorphisms in CYP2C9 have been shown to affect a patient's response to warfarin therapy (Reference 107). Specifically, Asian patients have been shown to require lower doses of warfarin because of the underexpression of *VKORC1* (Reference 108). Currently, no data are available to guide pharmacogenomic dosing of warfarin specifically in pediatric patients (Reference 90). In addition, factors other than pharmacogenomics may better explain the variation in warfarin dose in the pediatric patient population (Reference 103). Adverse events with warfarin primarily consist of bleeding complications, with other complications (thrombosis, "purple toe syndrome") occurring rarely (Reference 9). Studies evaluating the outpatient management of warfarin in pediatric patients have reported the incidence of bleeding caused by warfarin at around 0.5% per patient-year, although this rate can vary because of differing management strategies (References 9, 73, 89, 109). Guidelines for the reversal of warfarin therapy have been published, and reversal can be accomplished with the administration of enteral or intravenous vitamin K (Reference 8) (Table 2). Severe bleeding events may require the administration of blood products or recombinant clotting factors (References 8, 110). Routine administration of vitamin K for the management of elevated INR values without bleeding symptoms is discouraged. Holding warfarin therapy for a period is often as effective as administering reversal agents and prevents resistance to warfarin when therapy is reinitiated (Reference 111).

Unfractionated Heparin

Unfractionated heparin (UFH) is a glycosaminoglycan that potentiates the action of antithrombin III on thrombin (factor II) to inhibit the conversion of fibrinogen to fibrin, which leads to decreased formation of thrombi. Unfractionated heparin also releases tissue factor pathway inhibitor, which has antithrombotic effects (Reference 112). In addition, UFH inhibits the activated factors IX, X, XI, and XII and plasmin. Metabolism of UFH is thought to occur by the reticuloendothelial system, but it may have a small degree of elimination by renal routes (Reference 112).

Dosing of UFH is often dependent on laboratory monitoring parameters, patient factors, and pathophysiology (Table 1). Primarily, UFH is given as an intravenous continuous infusion for the treatment of thrombi, with loading doses given as a bolus. The subcutaneous route has been used for DVT prophylaxis in adults, but it is not typically recommended in children. Continuous infusions of UFH are dosed as units per kilogram per hour, with neonates requiring larger per kilogram doses compared with older children and adults, likely because of differences in heparin-protein–binding characteristics (References 69, 112, 113) (Table 1). Obese patients have been noted to require lower doses of UFH, but dose adjustment before therapy initiation for obesity is not routinely recommended (Reference 114). For patency of intravenous or intra-arterial catheters, UFH is usually administered at a constant continuous infusion through the catheter, with no dose adjustment on

Table 2. Reversal of Supratherapeutic Anticoagulant Effect (References 1, 4)

Anticoagulant	Laboratory Values	Clinical Evidence of Bleeding	Reversal Agent and Dosing
Low-molecular-weight heparin (enoxaparin)	Elevated aPTT or anti-Xa	Dependent on patient scenario—clinical evidence of bleeding not necessary to administer reversal agents	Protamine sulfate Dose for correction of enoxaparin overdose is 1 mg of protamine per 1 mg of enoxaparin. Additional doses of 0.5 mg of protamine per 1 mg can be administered at 2- to 4-hour intervals if necessary.
Unfractionated heparin	Elevated aPTT or anti-Xa	Dependent on patient scenario—clinical evidence of bleeding not necessary to administer reversal agents	Protamine sulfate Dose for immediate correction of UFH overdose is 1–1.5 mg of protamine per 100 units of UFH, with a maximum of 50 mg. UFH is rapidly eliminated, and protamine dose should be decreased on the basis of the time after UFH administration.
Warfarin	INR < 5	No evidence of bleeding	Hold doses – no reversal agent necessary
	INR ≥ 5 and < 9	No factors for increased bleeding risk and no evidence of bleeding	Hold doses – no reversal agent necessary
	INR ≥ 9	Factors that increase risk of bleeding but no evidence of bleeding	Hold doses – administer enteral vitamin K at 1–2.5 mg/dose daily until INR is within normal limits.
		No bleeding	Hold doses – administer enteral vitamin K at 2.5–5 mg/dose daily until INR is within normal limits.
	Any INR value	Serious or life-threatening bleeding	Hold doses – administer intravenous vitamin K, fresh frozen plasma, cryoprecipitate. Recombinant factor VIIa (10-100 mcg/kg/ dose) may also be used. Lower doses are initially preferred.

anti-Xa = antifactor Xa; aPTT = activated partial thromboplastin time; INR = international normalized ratio; UFH = unfractionated heparin.

the basis of laboratory parameters (Reference 8). Bolus doses of UFH can be used to flush intravenous catheters (Reference 8). Caution should be exercised and institutional safety policies developed when using UFH for various indications in the inpatient setting. Serious errors have occurred because of several concentrations of commercially available UFH.

Laboratory monitoring of UFH can vary markedly depending on patient care setting and availability of tests (Table 1). Traditionally, the activated partial thromboplastin time (aPTT) has been the standard for laboratory measurement of therapeutic effect of UFH. The aPTT is titrated to an antifactor Xa (anti-Xa) concentration of 0.3–0.7 unit/mL (chromogenic assay). Antifactor Xa concentration monitoring in pediatric patients is used in some institutions, but it is not routinely available because of cost and labor (References 112, 113, 115–120). The activated clotting time (ACT) is used when heparin concentrations are high, as in patients in the cardiac catheterization laboratory or patients on cardiopulmonary bypass or extracorporeal membrane oxygenation. Overall, the ideal laboratory monitoring parameter for UFH in pediatric patients is unclear. The use of the aPTT or the ACT for children has not been shown to correlate well with anti-Xa concentrations (References 115, 116, 119–121). Finally, there have been no data to correlate beneficial outcomes with the achievement of goal aPTT values in pediatric patients (Reference 112).

Primary adverse events with UFH are bleeding and heparin-induced thrombocytopenia (HIT). Bleeding rates in pediatric patients receiving UFH are high (ranging from 1% to 56% of patients), but they are difficult to interpret because of the variety of definitions used and the relative paucity of data (Reference 112). Nonetheless, bleeding is a common adverse event in pediatric patients receiving UFH, and neonates or critically ill children may be at a greater risk of hemorrhage. Clinically significant hemorrhage can be treated with protamine sulfate and by discontinuing the UFH infusion (Table 2).

Heparin-induced thrombocytopenia type II is an immune-mediated reaction to platelets, whereas HIT type I is a much milder form of thrombocytopenia that is not immune mediated. Heparin-induced thrombocytopenia type II is characterized by a greater than 50% decrease in platelets and/or a new thrombotic event after the initiation of UFH, typically 5–14 days after starting (Reference 122). Clinical confirmation of HIT type II can occur with laboratory testing (serotonin tests, platelet factor 4, ELISA [enzyme-linked immunoassay]); however, the sensitivity and specificity of these tests are often low, and the results can be inconclusive. The data for HIT type II in pediatric patients are scarce, but it is thought to occur at a much lower incidence than in adult patients (Reference 123). When a patient is given a diagnosis of HIT type II, removal of UFH from all sources, including flushes, must occur. A direct thrombin inhibitor can be used, if anticoagulant therapy is necessary. However, low-molecular-weight heparins should not be used because of a high incidence of cross-reactivity (Reference 124).

Finally, osteoporosis has been noted as a potential adverse event in patients who are receiving prolonged therapy with UFH (Reference 125). It is recommended that long-term therapy with UFH be avoided to minimize the risk of osteoporosis (Reference 112).

Low-Molecular-Weight Heparin

The primary low-molecular-weight heparin used in pediatric patients is enoxaparin. Other low-molecular-weight heparins, such as dalteparin and tinzaparin; have limited data for use in pediatric patients (References 126, 127). Enoxaparin primarily inhibits factor X and, to a lesser degree, factor II, by potentiating the action of antithrombin III on those factors. Factor X is inhibited to a 4 times greater extent than factor II. Enoxaparin is renally eliminated, with as much as 40% of the drug eliminated unchanged in the urine (References 69, 128–130). Enoxaparin has high bioavailability (about 100%) when administered subcutaneously (Reference 69).

Dosing of enoxaparin for treatment of thrombosis is on a milligram per kilogram basis for children (References 69, 128) (Table 1). An upper limit of dosing has not been determined, but morbidly obese patients may require empiric decreases in dose (References 131, 132). Dosage requirements to attain therapeutic concentrations decrease with age, with neonates requiring higher doses per kilogram than older children and adults (References 69, 128, 130, 133–139). However, the dose requirements for neonates and infants can vary widely (References 69, 128, 130, 133–139). Because enoxaparin is renally eliminated, patients with renal dysfunction or those who are undergoing dialysis should have doses adjusted on the basis of anti-Xa monitoring (Reference 69). To decrease the pain associated with several injections, subcutaneous catheters have been used (References 133–136). The catheter can be placed subcutaneously and enoxaparin injected through the catheter, thus minimizing breaks into the skin. Dilutions of enoxaparin made from commercially available concentrations and the use of insulin syringes have been proposed to ensure adequate delivery of small volumes for subcutaneous injection (References 140, 141).

Antifactor Xa monitoring is not typically indicated for adult patients without significant comorbidities or in adult patients who receive enoxaparin for DVT prophylaxis. Patients with renal dysfunction, pregnancy, or obesity should have concentrations monitored because all of these can affect the attainment of therapeutic concentrations (Reference 69). In addition, pediatric patients should have anti-Xa concentrations monitored because of the wide range of dosing, particularly in neonates and infants, to achieve therapeutic concentrations and minimize bleeding risk (References 128, 136, 137). An anti-Xa concentration of 0.5–1 unit/mL drawn 4–6 hours after a dose at steady state is generally considered a therapeutic concentration, although there are limited pediatric data confirming the efficacy of this range (References 142, 143) (Table 1).

Bleeding has been associated with enoxaparin use, but at a much lower rate than with UFH. Hematoma development at the site of subcutaneous injection has been noted to occur, and appropriate administration techniques can minimize this adverse event (References 141, 144). Protamine sulfate can be used to reverse the effects of enoxaparin (References 69, 145) (Table 2). Heparin-induced thrombocytopenia has been noted with enoxaparin, but at a lower incidence than with UFH (Reference 69). However, low-molecular-weight heparins should not be used in patients who have developed HIT type II while receiving UFH.

Alteplase

Alteplase is a recombinant form of serine protease that activates the conversion of plasminogen to plasmin within a fibrin clot. The plasmin degrades the fibrin and other procoagulant materials into soluble materials, thereby reducing the fibrin thrombus. Adult data suggest that alteplase has a very short half-life (from a few minutes to an hour) and that it is primarily hepatically metabolized. Few pharmacokinetic data are available to guide alteplase dosing in pediatric patients (Reference 69).

Alteplase dosing for the treatment of a thrombus in pediatric patients is controversial. High- and low-dose regimens have been reported (References 68, 69, 146–161) (Table 1). The clinical condition of the patient, size and location of the thrombus, and comfort of the practitioner in using alteplase may all be factors that determine the regimen chosen.

When administered systemically, alteplase is often given as an adjunct to continuous-infusion UFH therapy to prevent the re-formation of thrombus after lysis. Patient platelet counts, plasminogen levels, fibrinogen levels, aPTT, and anti-Xa levels should be monitored during the course of alteplase therapy. Patients should be monitored for signs and symptoms of bleeding, and they should be evaluated for bleeding risks before therapy is initiated.

When alteplase is used to clear an occluded arterial or venous catheter, standard doses and concentrations are often instilled into the occluded catheter, with lower doses/concentrations administered to younger patients. The alteplase is instilled into the catheter, left to dwell for about 2 hours, and then aspirated from the catheter and not given to the patient (Reference 69). Laboratory monitoring is not indicated when alteplase is used in this situation.

Abciximab

Abciximab is an intravenous glycoprotein IIb/IIIa platelet inhibitor, used commonly in adult patients undergoing interventional cardiac catheterization procedures (Reference 162). Abciximab, which is given as a continuous infusion, is a potent, long-term, platelet inhibitor (Reference 69). Half-life in adults has been reported at about 30 minutes (Reference 69). Bleeding is the primary potential adverse event.

Pediatric data are limited to the use of abciximab in patients with Kawasaki disease (to prevent coronary remodeling) and a case report of its use to prevent thrombus on a device placed in the cardiac catheterization laboratory (References 163–166) (Table 1). Future reports on the use of abciximab in pediatric patients are needed before routine use can be recommended.

Bivalirudin

Bivalirudin is an intravenous direct thrombin inhibitor, with an immediate onset of action and a half-life of about 25 minutes in adults (Reference 72). The primary reported adverse events have been bleeding and hypotension in adults. The dose should be reduced for patients with kidney dysfunction to prevent accumulation of the drug (Reference 72) (Table 1). Therapy should be monitored using the ACT, particularly in areas where that test is the standard of care (i.e., cardiac catheterization laboratory).

Bivalirudin has shown promise in pediatric patients as an alternative to UFH in patients with HIT or other coagulopathies (References 122, 167–171). Dosing of bivalirudin in pediatric patients appears to be similar to that of adult patients, with good evidence of efficacy in treating thrombi (References 172, 173) (Table 1).

Argatroban

Argatroban is an intravenous direct thrombin inhibitor with a fast onset of action and a short half-life after the continuous infusion is discontinued (Reference 69). About 20% of the drug is eliminated through the urine unchanged, but no empiric adjustment for kidney dysfunction is currently recommended (Reference 69). A dose adjustment for severe hepatic dysfunction is recommended (Reference 69). A considerable body of literature in pediatric patients has been reported, and pharmacokinetic studies have been performed (References 174–176). It has been noted that critically ill pediatric patients have a lower clearance (up to 50% lower) than a relatively healthy adult patient; these patients may therefore require dose adjustments accordingly (Reference 174).

The literature for pediatric patients has primarily been in the form of case reports or series of patients with HIT requiring mechanical circulatory support (References 177–183) (Table 1). Other reports have shown its use in pediatric patients in the cardiac catheterization laboratory (Reference 184). Higher-goal INR values must be used when changing a patient from argatroban to warfarin because argatroban will elevate INR values (Reference 69). In this scenario, argatroban should typically not be discontinued until the INR value is greater than 4 (Reference 69). Argatroban therapy should be monitored with aPTT, in general, or with ACT if being used in the cardiac catheterization laboratory, in patients on extracorporeal membrane oxygenation, or during cardiopulmonary bypass (Reference 69). Specific monitoring strategies for pediatric patients may vary with institutional practices and patient pathophysiologies.

Future Directions

Agents such as clopidogrel are coming to the forefront of therapy for treatment and prevention of thromboembolism in pediatric patients (References 39, 77, 185). As more experience is gathered, the ability to identify patients who will benefit the most from clopidogrel will be easier. Other agents such as dabigatran, an oral direct thrombin inhibitor, may be used more when clinical trials delineating pharmacokinetic and pharmacodynamic parameters in pediatric patients are completed (References 186, 187). Rivaroxaban, an oral direct factor Xa inhibitor, may also be used more in pediatric patients in the future (Reference 188).

Conclusions

Anticoagulation of pediatric patients is challenging and requires expert knowledge. Pharmacists who care for pediatric patients should not only understand the pharmacology of anticoagulant and antiplatelet agents in infants and children, but also be aware of the limitations in the data for their use.

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CHAPTER 49

Hemophilia A and B

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Learning Objectives

1. Discuss the differences between hemophilia A and B with respect to incidence and treatment options.
2. Describe inhibitors and their impact on therapy.
3. Identify complications associated with hemophilia and treatment of hemophilia.

Abbreviations in This Chapter

aPCCs	Activated prothrombin complex concentrates
BU	Bethesda unit
FVIII	Factor VIII
FIX	Factor IX
ICH	Intracranial hemorrhage
ITI	Immune tolerance induction
PCCs	Prothrombin complex concentrates
rFVIIa	Recombinant activated factor VII

Introduction

Hemophilia A and B are genetic bleeding disorders that result from decreased or absent circulating levels of functional factor VIII (FVIII) or factor IX (FIX), respectively. This deficiency can ultimately lead to prolonged and excessive bleeding and result in poor-quality clot formation. Hemophilia A (also known as classic hemophilia) is more common and accounts for 80% to 85% of cases or 1 in 5,000–10,000 males. Hemophilia B (also known as Christmas disease, named for the first patient identified) constitutes the remaining 15% to 20% of cases or 1 in 30,000–50,000 males (References 1–3). Hemophilia A and B occur in all ethnic groups.

Etiology

Both hemophilia A and B are genetically inherited X-linked recessive disorders primarily expressed in males. Women have two X chromosomes; therefore, if one is affected, the other carries the information for normal factor production, and the woman does not exhibit signs or symptoms of the disease. Any female children from a mother who is a carrier have a 50% chance of also being a carrier for the disease. Any male children have a 50% chance of receiving the affected X chromosome resulting in hemophilia. Every female child from a father with hemophilia will be a carrier for the disease. Despite the genetic inheritance of hemophilia, about one-third of patients with newly diagnosed hemophilia have no family history of the disease, indicating a spontaneous genetic mutation (Reference 1).

The FVIII and FIX genes are located on the long arm of the X chromosome. These genes are very long and complex, representing around 0.1% of the X chromosome. Many mutations have been identified, including gene deletions, stop codon abnormalities, frameshift mutations, and inversion mutations. The inversion of intron 22 is the most common mutation found in hemophilia A (about 50%) and can be identified using Southern blot analysis (Reference 1). Independent mutations account for greater than 95% of all families with severe or moderate hemophilia B. Missense mutations are the most common mutations in patients with hemophilia B, accounting for 60% of FIX defects (Reference 4). Knowledge of the gene mutations may be used for determining carrier status and prenatal assessment. Major alterations to either gene will lead to a more severe disease compared with minor defects. Mutations in the 5' promoter region can result in the hemophilia B Leiden phenotype, which is characterized by very low levels of FIX activity at birth and through childhood but increases in adolescence to greater than 60% after puberty in response to androgens (Reference 1).

Acquired hemophilia is an autoimmune disease targeting FVIII and is very uncommon in children. The production of autoantibodies leads to FVIII proteolysis, thus increasing plasma clearance (Reference 5). Bleeding complications, which present similarly to classic hemophilia, are unpredictable. Fifty percent of cases occur spontaneously, whereas 10% occur postpartum within 3 months of delivery (Reference 5). Autoantibodies can be transferred to the neonate across the placenta, which can result in clinically significant bleeding. The incidence of acquired hemophilia is equally distributed between men and women. Outcomes are generally better in children because of the quicker resolution of autoantibodies in cases secondary to infections or antibiotic use (Reference 5).

Pathophysiology

Both FVIII and FIX are crucial for normal thrombin formation. The classic representation of hemostasis is through activation of factor X by factor VII and tissue-activating factor. However, recent studies suggest that

FIX plays a role in this activation sequence. Through the intrinsic pathway, activated FIX complexes with activated FVIII, calcium, and phosphatidylserine on the membrane surface to generate activated factor X. The activation of factor X initiates the common pathway of the coagulation cascade, leading to normal thrombin and fibrin generation (Reference 4). A deficiency of FVIII or FIX results in delayed formation of a clot caused by a lack of normal thrombin and fibrin production (Figure 1). The resulting clots are friable, and re-bleeding is common. About 50% of patients with hemophilia B produce a nonfunctional FIX protein, whereas the rest of patients lack production of the protein entirely.

Diagnosis

Mothers with known familial hemophilia may have sons tested with a cord blood FVIII or FIX activity assay obtained at the time of delivery because neither FVIII nor FIX crosses the placenta. Prenatal testing may be performed using chorionic villus sampling or amniocentesis (Reference 1). These invasive techniques are not without risk to the mother and the fetus and should be discussed with the parents before the procedure.

About one-third of patients with a new diagnosis have no known family members with the disease. Children with signs of bleeding that are suggestive of hemophilia are evaluated further to make the diagnosis. These signs may include prolonged bleeding in newborns with circumcision or heel sticks, intracranial hemorrhage (ICH) or large cephalohematomas after difficult vaginal deliveries (e.g., use of forceps or vacuum extraction), or large raised bruising and/or an unusual number of bruises. Common laboratory parameters include a complete blood cell count, coagulation studies, and FVIII and FIX assays. Most patients with hemophilia have significantly prolonged partial thromboplastin time (PTT) (Reference 5). In general, the PTT is thought to be the most sensitive measure of defects in the intrinsic pathway of the coagulation cascade.

The severity of hemophilia is based on the patient's baseline circulating functional FVIII or FIX activity (Table 1). One unit is defined as the amount of factor found in 1 mL of normal plasma. Factor levels are often expressed as a percentage of activity. A level of 100% (1 IU/mL) is equal to the activity in 1 mL of normal plasma (Reference 4). For hemophilia A, around 70% of patients have the severe form of the disease. For hemophilia B, the prevalence of the severe form is around 50% (Reference 7). The diagnosis of mild hemophilia in a newborn may be delayed because vitamin K–dependent factors are reduced in this patient population and therefore would naturally have a slightly prolonged PTT (Reference 5).

Clinical Manifestations

The clinical manifestations of hemophilia A and B are all associated with bleeding. Patients with the severe form of the disease often have bleeding episodes from minor or unknown trauma. These children will often have spontaneous bleeding into muscle or joints from one to six times/month. If bleeding occurs in a closed space, such as a joint, cessation is aided by tamponade. In contrast, an open wound in which tamponade cannot occur may result in substantial blood loss (Reference 4). Patients with the moderate classification of the disease will not spontaneously bleed but can have significant bleeding with mild to moderate trauma. Those with only mild hemophilia may be undiagnosed for many years and have significant bleeding only with severe trauma or surgery (Reference 4). The significance of the bleeding will be determined by the location and severity of disease.

Central Nervous System Bleeds

Bleeding into the central nervous system can be a life-threatening situation for a patient with hemophilia. Because FVIII and FIX do not cross the placenta, male infants with the severe form of the disease will

Table 1. Categorization of the Severity of Hemophilia

Severity	Clotting Factor Level % activity (IU/mL)	Bleeding Risk
Mild	5% to 40% (0.05–0.40)	Prolonged bleeding only with severe trauma or surgery
Moderate	1% to 5% (0.01–0.05)	Spontaneous bleeding is rare. Prolonged bleeding with trauma or surgery
Severe	< 1% (< 0.01)	Spontaneous bleeding

Created from Reference 6.

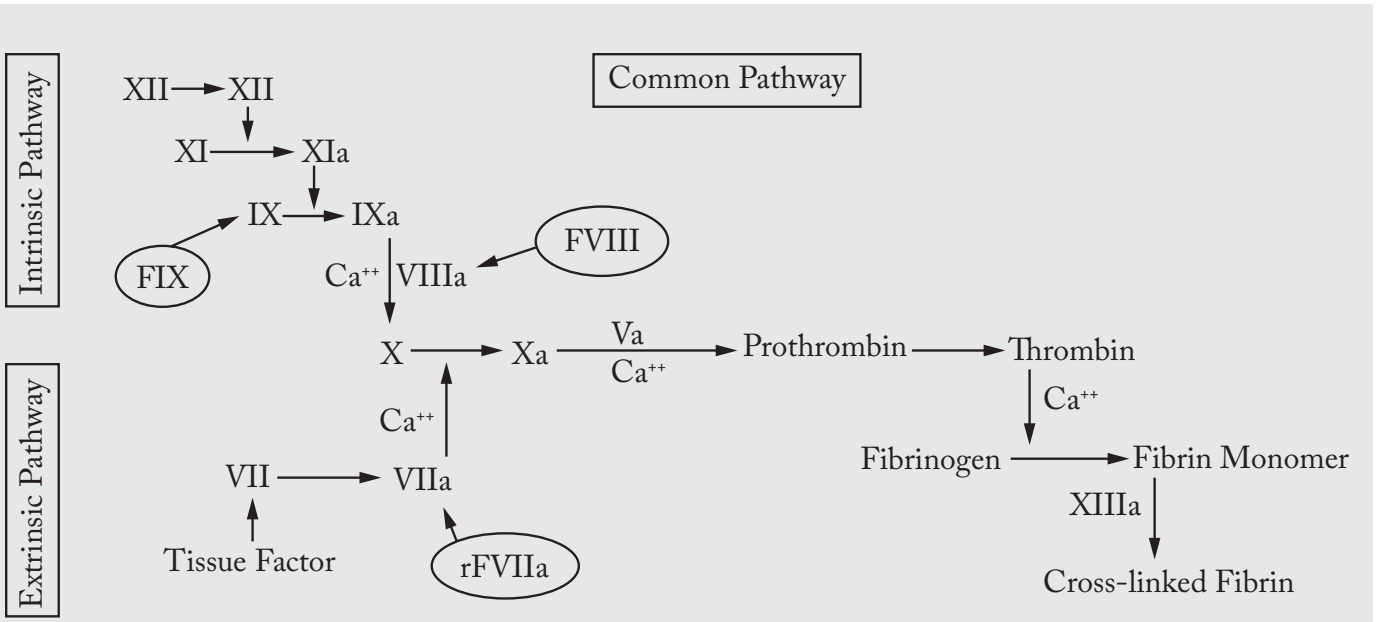


Figure 1. Clotting cascade and hemophilia factors.

FIX = factor IX; FVIII = factor VIII; rFVIIa = recombinant activated factor VII.

have either no or very little FVIII or FIX at birth. Babies who are born after a long, difficult labor, or after a vaginal delivery aided by the use of forceps or vacuum extraction, are at risk of developing large cephalohematomas or ICHs. The signs of ICH can include pallor, lethargy, neurologic deficits, unequal pupils, tense fontanelle, or vomiting. If the type of hemophilia is not known and FVIII or FIX assays are not immediately available, fresh frozen plasma should be administered at a dose of 10 mL/kg of body weight (Reference 1). In some reports, around 1% to 2% of neonates with hemophilia experience an ICH.

Mucocutaneous/Soft Tissue Bleeds

In children without a family history of hemophilia, the disease is often diagnosed when the child begins to crawl or walk. Tongue and mouth ulcerations may occur around this time caused by the child's propensity for putting objects in his or her mouth. Soft tissue bruising is also more common during this first year of life, but it is often more alarming in appearance than clinically serious. If a diagnosis of hemophilia has not yet been made, these patients may be mistaken for child abuse victims. Around 30% of patients with hemophilia have bleeding with circumcision (Reference 5).

Hemarthrosis

As a toddler starts to maintain an upright position and transitions to walking, more pressure is placed on the ankles, making them one of the more frequent bleeding sites. After the ankles, the knees are the most common sites of joint bleeding. As the child ages, more bleeding will occur in the knees and elbows. When bleeding into a joint occurs, patients have described a sensation of tingling or warmth followed by increasing pain and decreased range of motion. In older children and adolescents, the risk of bleeding comes from sports-related activities and risk-taking behaviors. It usually takes 3–4 weeks for the blood to be reabsorbed from the joint and the fluid to be removed by the synovium (Reference 7).

When repeated bleeding occurs at a rate that does not allow this resolution back to baseline, the joint becomes a "target" for rebleeding, which is then identified as a "target" joint. These joints show a chronic inflammation of the synovium, which increases the volume of the joint. A new network of capillaries forms underneath the inflamed synovium to increase the blood flow for the removal of the breakdown products of the blood. The surface of the synovium becomes friable and irregular, increasing the likelihood of being caught in the sliding surfaces of the joint and causing more bleeding. This self-perpetuating process can lead to irreversible damage to the joint, resulting in loss of mobility, chronic pain, and ultimately destruction of the joint (Reference 7). Splinting and application of ice packs to the affected joint may provide some pain relief, but these are no substitute for factor replacement therapy (Reference 5). Medications such as aspirin and ibuprofen inhibit platelet function and can further hinder hemostasis in patients with hemophilia; therefore, these medications should be avoided. Early and aggressive management of these bleeds is the best approach for preventing the

bleed-synovitis-bleed cycle that characterizes a target joint. In patients with target joint bleeds that cannot be controlled with appropriate prophylactic factor administration, it may be necessary to remove the affected synovium, allowing a new, normal synovial layer to form within a few weeks. This can be accomplished through surgical removal of the affected synovium or through injection of a chemical, such as rifampin, or a radioactive agent, such as yttrium (^{90}Y) (Reference 7).

Intramuscular Hemorrhage

Muscle hematomas may be difficult to diagnose because the bleeds are generally deep within the tissue and not easily palpable. Some children with severe hemophilia may have excessive bleeding after intramuscular vaccinations. The bleeding occurs in the body of the muscle, causing the affected area to swell. Patients report a vague feeling of pain with motion. Bleeding into muscles is as serious as bleeding into joints. Repeated muscle bleeds can result in severe muscle contractures caused by fibrosis and atrophy. Muscle weakness is also a risk factor for joint bleeds, thus continuing the cycle of complications. Appropriate factor replacement is necessary to stop the bleed and reduce the size of the hematoma, whereas physical therapy can restore range of motion and prevent fibrosis of the muscle (Reference 5).

One muscle that is particularly worrisome for bleeding is the iliopsoas muscle. Symptoms may be vague, including lower abdominal or upper thigh pain, pain with passive extension of the thigh, and paresthesias below the inguinal ligament from femoral nerve compression. The clinical diagnosis should be confirmed with either ultrasonography or computed tomography (CT). Iliopsoas muscle hemorrhages can be life threatening because of the large amount of blood volume that can be lost into the retroperitoneal space.

Bleeding into other flexor muscles such as the calf or forearm can lead to a process called "compartment syndrome." This is because of the limited space in the compartment where these muscles are located. When hemorrhage and swelling occur in this space, pressure compresses nerves and blood vessels that travel through the same compartment. This is manifested as paresthesias or numbness. Immediate factor replacement is indicated, and fasciotomy may be necessary if vascular supply and nerve function become compromised (Reference 8).

Treatment

The fundamental treatment of both hemophilia A and B is replacement of the deficient factor. The first recorded successful treatment of hemophilia using a blood transfusion was in 1840 (Reference 1). Since then, the treatment has evolved from the infusion of pork or bovine plasma, which caused allergic responses and limited its usefulness, to human pooled plasma products, which may expose the patient to transmission of bloodborne infectious risks such as hepatitis and human immunodeficiency virus (HIV), to our current practice of infusing safer, more pure factor concentrates produced through recombinant DNA technologies.

The improvements in replacement factors have made a dramatic impact on life expectancy for patients with hemophilia. The life expectancy before 1960 was a dismal 11 years for patients with severe hemophilia. From the 1960s to the early 1980s, this increased dramatically to about 60 years because of the development of replacement factors. During the 1980s, viral contamination of plasma-derived factor products became a problem. Many patients treated with these products became infected with HIV or hepatitis A, B, or C. The most serious of these was HIV, with 75% seroconversion in patients with severe hemophilia. In the United States, the mortality rates for patients with hemophilia tripled from 0.4 deaths per 1 million people (1979–1981) to 1.2 deaths per 1 million people (1987–1989). Acquired immunodeficiency syndrome (AIDS) accounted for 55% of all hemophilia deaths. With improved screening of donors, new purification methods, and recombinant factor production, much of this risk has been removed (References 9–11).

Despite these advances, apprehension remains as prions, such as Creutzfeldt-Jakob disease, emerge as a threat to patients with hemophilia who use blood- and plasma-derived products. Immunoaffinity and other chromatography techniques for preventing the transmission of prions are not well defined, and using pasteurization and solvent/detergent techniques is probably ineffective at preventing the transmission of these types of pathogens. In addition, other pathogens such as parvovirus B19 are resistant to many purification measures. The concern exists that there may be as-yet unidentified pathogens that can still be transmitted, even through highly purified products (Reference 12).

Early Therapies

Fresh frozen plasma was the only product available to treat hemophilia B until the introduction of prothrombin complex concentrates (PCCs) and activated PCCs (aPCCs) in 1972 (Reference 2). PCCs contain only the factors themselves, whereas aPCCs contain the factors as well as other activating components that allow hemostasis to occur through the common coagulation pathway. These are intermediate-purity pooled plasma products containing FIX and a variety of other vitamin K–dependent clotting factors (II, VII, and X). Although these hemostatic agents are highly effective for both hemophilia A and B, the PCCs, especially the aPCCs, have been associated with thrombotic complications, such as disseminated intravascular coagulation and myocardial infarction (Reference 2). Factor eight inhibitor bypass

activity (FEIBA) is one of the most commonly used aPCCs currently on the market. It has been activated during the fractionation process to achieve increased amounts of activated FVII, FX, and thrombin (Reference 4). The simultaneous use of antifibrinolytic therapy should be avoided in patients receiving this product because of an increased risk of thrombosis.

Factor Replacement Products

The cloning of the FVIII and FIX genes in the 1980s, combined with the explosion of recombinant technologies, led to the development of much safer, more consistent factor replacement products (Reference 13). Recently, newer techniques have been developed that allow recombinant FVIII (rFVIII) and recombinant FIX (rFIX) to be produced through a virtually plasma-free process. First-generation recombinant factor products employed viral removal or inactivation techniques, such as immunoaffinity or ion exchange chromatography (Reference 12). Second-generation recombinant factor products combined solvent/detergents and the use of ultra- or nano-filtration in their manufacturing process for the removal of enveloped viruses, such as HIV and hepatitis B and C (Reference 13). Third-generation recombinant factor products are manufactured through a process that is free of both human albumin and plasma (Table 2). Since 1999, rFIX has become the mainstay of therapy for hemophilia B.

Adjuvant Therapies

A nonpharmacologic adjuvant therapy for bleeds is easily remembered by the acronym RICE (rest, ice, compression, and elevation). Resting the joint or muscle associated with the bleed can be accomplished through splinting or the assistance of crutches or a wheelchair. Ice is helpful in reducing inflammation and causing vasoconstriction and should be applied to the area with a towel or wrap. It is recommended to apply ice or an ice pack for 20 minutes every 4–6 hours until pain and swelling begin to decrease (Reference 14).

The role of desmopressin in the treatment of hemophilia A involves patients with the mild to moderate form of the disease. Desmopressin causes bound FVIII to be released into the systemic circulation, elevating the concentration available for coagulation. This can be a useful home treatment for mild bleeds. Unfortunately, many patients may experience tachyphylaxis (diminishing response) with frequently repeated dosing. This can occur after just a few doses; therefore, if the bleeding does not resolve after one or two doses, replacement of FVIII is indicated. Because of the potential for hyponatremia and water intoxication, fluids should be restricted for at least 12 hours after a desmopressin dose. Because of the difficulty in restricting fluids in very young children, this drug is not recommended for use in children younger than 2 years. Desmopressin can be administered intravenously, orally, or intranasally. The last form is most often used for home therapy for hemophilia A. The concentrated nasal spray desmopressin (Stimate) delivers 150 mcg per activation. One spray of this product (one nostril) is recommended for patients weighing less than 50 kg and two sprays (one in each nostril) for those weighing 50 kg or more (References 15, 16).

Antifibrinolytic agents may be used in combination with factor replacement to help maintain a clot that has formed. This is most often seen with bleeds that occur in the oral cavity because these tissues are rich in fibrinolytic materials. The two products currently used are aminocaproic acid and tranexamic acid. They should be started the evening before any planned invasive dentistry

Table 2. Comparison of Recombinant Factor VIII Products

Product	Generation	Producing Cell Line	Stabilizing Agent	Purification Method
Recombinate	First	Chinese hamster ovary	Human albumin	Immunoaffinity, ion exchange
Kogenate FS/ Helixate FS	Second	Baby hamster kidney	Sucrose	Immunoaffinity, ion exchange, solvent/ detergent, ultrafiltration
ReFacto	Second	Chinese hamster ovary	Sucrose	Immunoaffinity, ion exchange, solvent/ detergent, nano-filtration
Advate	Third	Chinese hamster ovary	Trehalose	Immunoaffinity, ion exchange, solvent/ detergent, plasma/albumin-free culture medium
Xyntha	Third	Chinese hamster ovary	Sucrose	Immunoaffinity, ion exchange, solvent/ detergent, nano-filtration

Created from References 12, 14.

Table 3. Treatment of Specific Hemorrhages in Hemophilia

Event	Hemophilia A FVIII Dosing (international units/kg) (% Correction)		Hemophilia B[a] FIX Dosing (international units/kg) (% Correction)		Comments
	First Dose	Dosing/ Schedule (every 12–24 hr)	First Dose	Dosing/ Schedule (every 12–24 hr)	
Hemarthrosis	40–50 (80% to 100%)	20–35 (40% to 70%)	20–50 (20% to 50%)	30–50 (30% to 50%)	Ice for 20 minutes, immobilize for 48 hr
Muscle or soft tissue hematoma	25–50 (50% to 100%)	20–25 (40% to 50%)	20–30 (20% to 30%)	20–30 (20% to 30%)	Ice for 20 minutes
Hematuria	20–35 (40% to 70%)	25–30 (50% to 60%)	25–50 (25% to 50%)	30 (30%)	Bed rest, prednisone 1–2 mg/kg/day
Gastrointestinal	35–50 (70% to 100%)	25–35 (50% to 70%)	50–100 (50% to 100%)	50–100 (50% to 100%)	Monitor CBC
Mucosal/dental	35–50 (70% to 100%)	25–35 (50% to 70%)	25–50 (25% to 50%)	25–50 (25% to 50%)	Local ice, aminocaproic acid 100 mg/kg every 6 hr
Head trauma, major surgery	50–75 (100% to 150%)	25–35 (50% to 70%)	50–100 (50% to 100%)	50–100 (50% to 100%)	Monitor levels

[a]When administering recombinant FIX, adjust dose by a factor of 1.2 for adults and 1.4 for children.
CBC = complete blood cell count; FIX = factor IX; FVIII = factor VIII; hr = hour(s).
Created from References 4, 15.

and be continued for 7–10 days. A mouthwash can also be made by mixing tranexamic acid with sterile water to make a 10% solution. This may be helpful after permanent tooth extractions (Reference 15).

Therapeutic Approaches

One approach to hemophilia treatment is the "on-demand" administration of replacement factors. Bleeding episodes are treated with factor replacement at a dose that is based on the bleeding site and the patient's weight. The desired percent correction of factor activity varies by location of bleeding or procedure. The most severe bleeding associated with ICH or surgical procedures would require a 100% correction. The amount of FVIII product required to achieve this is calculated on the basis that 1 IU/kg will raise the serum FVIII activity by 2%. Using this formula, the desired dose of FVIII replacement can be determined: units of FVIII required = weight (kg) × desired level (%) × 0.5 (Reference 6). Because FIX binds to sites in the endothelium, more of the product is required to achieve the same rise in activity. Therefore, the amount of FIX product required to raise the activity to a desired level is twice that of the FVIII product: weight (kg) × desired level (%) × 1. The rFIX product requires a dose adjustment of 1.2 (for adults) to 1.4 (for children) international units/kg to raise the activity level by 1% (Reference 6). The frequency of dosing FVIII and FIX is influenced by their respective half-lives. Infused FVIII has a half-life of between 3 and 6 hours during the initial equilibration with the extravascular spaces. The half-life then becomes closer to 12 hours. Dosing initially can be as frequent as every 8 hours until good hemostasis is achieved. The frequency can then be extended to every 12 hours, followed by every 24 hours as the patient recovers. The FIX product has a half-life of about 18–24 hours, allowing once-daily dosing except before surgery, when a twice-daily dose is required for the first day of the procedure (Reference 6). See Table 3 for common dosing goals. All factor products can be administered as rapid intravenous infusions over several minutes. Maximum infusion rates are specific to each product. Continuous infusion of FVIII is an approach that has been used in the treatment of moderate and severe bleeds. It has been shown that using a continuous infusion of factor after initial homeostasis is achieved can result in less overall factor consumption by avoiding the peaks and troughs associated with bolus dosing (Reference 17). An infusion rate of 2–3 IU/kg/hour can maintain an activity level of around 50% to 60% (Reference 4). Factor VIII levels should be monitored periodically to ensure goal levels are reached.

Therapeutic Monitoring

Most therapeutic monitoring of acute bleeding episodes is based on overall clinical response (Reference 18). The clinical monitoring of a patient with an acute bleed includes surrogate markers such as pain levels,

range of motion if the acute bleed is in a joint, swelling, and laboratory values such as hemoglobin. Although serum factor levels can be measured, the results can vary widely, and the clinical correlation is inconsistent. This is thought to be owing to the variable effect of FVIII on endogenous thrombin generation (Reference 19). The monitoring of factor VIII levels is warranted in the setting of surgical procedures. In some cases, homeostasis is achieved using a continuous infusion of factor product. Daily monitoring of factor levels during the continuous infusion is beneficial to ensure a consistent level of factor activity (Reference 20). Research continues into identifying the most appropriate surrogate marker for monitoring therapy. Parameters such as thrombin generation tests and endogenous thrombin potential are being studied to determine their degree of clinical correlation to outcomes (References 21, 22). If the patient is not clinically responding to adequate doses of factor replacement, serum should be sent for testing to determine whether an inhibitor is present.

Prophylaxis

Another approach to therapy for hemophilia A and B is the prophylactic administration of factor concentrates. At present, there is no agreed-on definition for prophylactic therapy. The European Paediatric Network for Haemophilia Management has suggested several definitions based on the initiation of therapy. They describe primary prophylaxis as continuous therapy starting before 2 years of age (solely on the basis of age) or after the first episode of hemarthrosis and before 2 years of age. Secondary prophylaxis can be a long-term continuous treatment started after 2 years of age and two or more joint bleeds, or it can be an intermittent periodic treatment approach (Reference 23). The ultimate goal of primary prophylaxis is to prevent the formation of target joints and subsequent chronic arthropathy. Secondary prophylaxis is intended to prevent the progression of joint disease. It is important to remember that even one severe hemarthrosis is enough to start the cycle of bleeding and synovial hypertrophy that leads to the formation of a target joint (Reference 6). However, MRI examinations have shown that sometimes abnormalities have already occurred, even if there has been no clinically recognized hemarthrosis event. Prophylaxis is now recommended by the World Health Organization and the World Federation of Hemophilia (References 6, 14). Factor VIII 20–40 international units/kg every other day or three times/week is given to maintain FVIII levels above 0.01 IU/mL (1%) to prevent spontaneous bleeding in patients with severe hemophilia A (References 24, 25). A prophylactic dose for hemophilia B would be FIX 25–40 international units/kg twice weekly because of the longer half-life (References 5, 6). The efficacy of this approach largely depends on the patient's adherence (Reference 26).

Until recently, primary prophylaxis was reserved for patients without inhibitors. Inhibitors are antibodies that can develop against the exogenously administered factor products, significantly decreasing their efficacy. A recent study compared on-demand therapy with prophylaxis using an aPCC (FEIBA) for patients with inhibitors. This prospective, randomized, crossover study was performed at 16 hemophilia treatment centers in Europe and the United States. A target dose of 85 units/kg was used for on-demand therapy as well as prophylaxis. The prophylaxis dose was administered on 3 nonconsecutive days weekly. The duration of on-demand therapy and prophylaxis was 6 months each, with a 3-month washout period in between. Twenty-six patients completed both study periods and were evaluable for the efficacy analysis. The overall reduction in bleeding was 84%, and the reduction in joint bleeds was 61%, with target joint bleeds reduced by 71% during the prophylactic period (Reference 27). These findings give clinical support to the use of bypassing agents for prophylaxis in children who develop inhibitors.

Despite the many studies establishing prophylaxis as a superior approach to treatment versus on-demand therapy, prophylaxis is not considered standard of practice by many institutions. The main deterrents continue to be cost and complications. The costs of prophylaxis versus those of on-demand therapy are difficult to quantify. The factor consumed during on-demand therapy tends to be one-third that consumed with the prophylactic approach (References 27, 28). However, when assessing the pharmacoeconomics of prophylaxis, it must be viewed from a long-term outcome perspective, including variables such as quality of life, potential benefits of avoiding hospitalizations and days lost from school or work, and prevention of long-term complications such as worsening joint disease and disability.

Another obstacle to prophylactic therapy is the need for venous access for factor administration. Peripheral venous access is preferred for the infusion of factor products; however, for patients receiving continuous prophylactic or immune tolerance induction (ITI) therapy, a central venous access device may be required. These are especially useful in infants and children whose small veins are difficult to access and who tend to be intolerant of frequent needlesticks. Central venous access devices are used in about 30% of children receiving prophylactic therapy and 90% of those receiving daily ITI (Reference 29). The biggest drawback to these devices is the risk of infection. A meta-analysis performed on 48 studies found a 44% incidence of infection in

patients with central venous access devices (Reference 30). These devices also require comprehensive education of the family/caregivers on proper aseptic technique as well as maintenance and monitoring of the central line.

Complications of Therapy

A serious complication of hemophilia therapy is the formation of antibodies against FVIII and FIX. Inhibitors neutralize the procoagulant activity of FVIII and FIX, leading to the failure of routine factor replacement therapy. About 14% to 35% of patients with severe hemophilia A and up to 3% of patients with severe hemophilia B will develop inhibitors (References 2, 4, 31). Most inhibitor development occurs in patients with severe hemophilia around 1–2 years of age with about 9–12 treatments with factor product. The highest risk of developing inhibitors occurs within the first 50 exposures to FVIII, with the risk rapidly reducing after 200 treatment days (Reference 32). Risk factors for developing inhibitors include genetic factors such as the type of mutation on the FVIII or FIX gene, polymorphisms in genes that regulate the immune system, family history of inhibitors, and African heritage (References 33–36). Environmental risk factors for inhibitor development include intensive factor exposure caused by serious injury, surgery, or immunologic challenge such as infection or immunizations (Reference 37). In addition to the loss of therapeutic response to factor replacement, patients with hemophilia B with inhibitor development may experience anaphylaxis associated with FIX administration (Reference 38).

Inhibitors can be categorized into two groups: low responding and high responding. Inhibitors are measured by the Bethesda assay. One Bethesda unit (BU) is defined as the amount of inhibitor needed to inactivate 50% of FVIII or FIX in pooled normal plasma. Low-responding inhibitors are defined by a peak historical titer of less than 5 BU/mL, resulting in a very low or attenuated response to FVIII or FIX (Reference 6). Patients with low-responding inhibitors may still respond to factor replacement therapy at higher doses and/or more frequent dosing intervals. High-responding inhibitors are those with a titer greater than 5 BU/mL or a brisk anamnestic response to FVIII challenge. Patients can convert from low-responding inhibitors to high-responding inhibitors over time. All patients should be monitored for inhibitor formation every 6 months or in the setting of a decreased clinical or laboratory response to therapy (Reference 6).

Patients with high-responding inhibitors usually will not respond to FVIII or FIX replacement therapy even at high doses, and alternative approaches to treatment of acute bleeds must be used, such as recombinant activated factor VII (rFVIIa) (90 mcg/kg every 2–3 hours) or aPCCs (FEIBA 50–100 international units/kg every 6–12 hours) (References 39, 40). Recombinant activated FVII achieves homeostasis without requiring FVIII or FIX using the extrinsic coagulation pathway, binding to tissue factor at the site of injury, which then triggers coagulation through the common pathway. It can also cause activation of FIX and factor X on the surface of activated platelets (Reference 6).

Once an inhibitor has formed, ITI may be initiated in an attempt to decrease or eliminate the antibodies. Immune tolerance induction involves frequent, continuing exposure to the deficient clotting factor to achieve tolerance by antigen overload, resulting in restoration of normal factor replacement pharmacokinetics (PK) (Reference 2). This approach was first attempted in the 1970s and was achieved by the administration of high doses of FVIII (100–150 international units/kg) twice daily with the combination of aPCCs for control of acute bleeds. After a period of months to years, the FVIII antibodies were markedly reduced, and the dose could be decreased to a smaller daily dose or even administered every other day (Reference 5). A variety of different ITI regimens have been developed, some using varied doses of FVIII given less frequently and others combining the use of intravenous gammaglobulin and immunosuppressants (cyclophosphamide, rituximab) (Reference 39). Immune tolerance induction success rates are generally higher in patients with lower inhibitor titers (preferably less than 10 BU) at the initiation of therapy (References 40, 41). A meta-analysis of the North American Immune Tolerance Registry (NAITR) and the International Immune Tolerance Registry (IITR) determined that for patients with inhibitor titers less than 200 BU and pre-ITI titers less than 10 BU, FVIII dose did not affect ITI outcome. The IITR study protocol is presently comparing high-dose ITI (200 units/kg/day) with low-dose (50 units/kg three times/week). The data are undergoing final analysis (Reference 40). In patients with hemophilia A, ITI is unsuccessful in 30% to 50% of individuals. Immune tolerance induction in patients with hemophilia B is much less effective, with a high incidence of allergic reaction. Immune tolerance induction is demanding and expensive, exceeding $1.2 million dollars for an average 5-year-old patient (Reference 42). The need for central venous access is another factor to consider when deciding whether to initiate ITI. However, the cost of successful ITI can decrease the overall lifetime cost of hemophilia therapy (References 6, 42, 43).

Some studies report better success rates for ITI in patients receiving plasma-derived factor products containing von Willebrand factor (VWF) (Reference 44), which is thought to be because of the role of VWF in FVIII function, stabilization, and immunogenicity. By VWF's binding to the C2 domain of FVIII, a

common site for inhibitor formation, epitope masking and decreased inhibitor activity may result. The use of VWF-containing products may also extend the plasma half-life of FVIII during ITI, thus increasing antigen presentation and possibly contributing to its overall success (Reference 44). If no response is seen after 2 years of ITI, the treatment approach is usually discontinued (Reference 6).

Future Considerations

Gene therapy for hemophilia A and B is being studied, but it is not yet available. Early success in animal models has been achieved; however, long-term maintenance of adequate clotting factors continues to be a problem (Reference 45). Current hemophilia research is focused in the areas of factor product improvement. One approach to improving factor products is through modification of the factor molecule to include polyethylene glycol (PEGylation). Polyethylene glycol can enhance the PK and pharmacodynamics (PD) of the factor product. These molecules would be less susceptible to proteolytic cleavage and degradation and would undergo slower clearance from the circulation, resulting in a longer half-life. Clinical studies are under way researching the possibility of PEGylation of rFVIII and rFVIIa. The PEGylation of rFIX has resulted in a product with an extended half-life, allowing once-weekly dosing (References 46–48). Another avenue of research is binding albumin to rFIX or rFVIIa to prolong half-life without increasing immunogenicity (Reference 49). Another mechanism for extending half-life has been created by fusing the Fc region of the immunoglobulin G to rFIX (rFIXFc) (Reference 50). Phase I studies have been concluded, and phase II/III studies are under way (References 45, 50).

Increasing the catalytic activity of a clotting factor may intensify its coagulation activity. Genetically engineered FIX molecules are under development. Intensifying the catalytic activity of a clotting factor may also improve the therapeutic index of gene therapy vectors for hemophilia B (References 51, 52). Bayer Healthcare is studying a "biosuperior" FVIIa molecule using a technology called DNA shuffling. This product has the ability to activate FX in the absence of tissue factor, resulting in a more potent product. Modifications were then made to improve its platelet targeting ability to make it less thrombogenic. Bayer also increased the number of *N*-glycosylations to prolong the half-life of the factor product. In animal studies, one candidate molecule (BAY866150) showed improved PK and PD parameters as well as an in vitro thrombin burst. A phase I study of patients with hemophilia A and B with inhibitors is planned (Reference 2).

Conclusions

From the transfusion of blood products to the development of recombinant factors to the creation of genetic therapies, the treatment of hemophilia continues to evolve. It has changed from a childhood disease with early mortality to a chronically managed disease with a significantly improved life span. As the options for therapy continue to grow, the life span and quality of life continue to improve for patients affected by the disease.

It is essential that pharmacists take an active role in understanding the treatment regimens as well as the products available for managing hemophilia A and B. A complete understanding of the pathophysiology of the disease is also necessary to assist patients with supportive care both inside and outside the hospital setting. Important advances in hemophilia A and B therapies have occurred during the past 25 years, resulting in safer treatment options, better quality of life for patients, and, with improvements in gene therapy on the horizon, hope for a cure in the future.

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CHAPTER 50

Pediatric Sickle Cell Disease

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Learning Objectives

1. Discuss the role of newborn screening in sickle cell disease (SCD).
2. List the signs and symptoms of SCD for infants, children, and adolescents.
3. Recognize the clinical characteristics associated with an acute sickle cell crisis.
4. Identify patients who require penicillin prophylaxis.
5. Explain the rationale for the use of hydroxyurea in pediatric patients with SCD.
6. Identify appropriate hydroxyurea regimens and monitoring parameters.
7. Discuss the risks and benefits of chronic transfusion therapy in patients with SCD.
8. Select appropriate empiric antimicrobial coverage in children with SCD who present with fever.
9. Develop a treatment plan for chelation therapy in pediatric patients receiving chronic transfusion therapy.
10. Create a treatment plan for children and adolescents with SCD who present with acute chest syndrome, priapism, and sickle cell crisis.
11. Devise a pain management plan for pediatric patients presenting with vaso-occlusive pain crisis.

Abbreviations in This Chapter

ACS	Acute chest syndrome
HbA	Normal adult hemoglobin
HbF	Fetal hemoglobin
HbS	Sickle hemoglobin
HbSC	Compound heterozygous (HbS and hemoglobin C)
HbSS	Homozygous form of SCD
HLA	Human leukocyte antigen
RBCs	Red blood cells
SCD	Sickle cell disease
SCT	Sickle cell trait

Introduction

Sickle cell disease (SCD) is one of the most commonly inherited diseases in the United States, primarily affecting African Americans. About 2,000 confirmed cases are reported through neonatal screening in the United States each year (Reference 1). Although childhood morbidity and mortality have dramatically decreased because of standardized newborn screening, advances in preventive therapy, and acute complication management, children with SCD are often hospitalized, usually for severe pain, fever, or acute complications. Sickle cell disease is a chronic illness that can have a detrimental effect on a child's quality of life and, because of its unpredictability, can lead to interruptions in children's physical, family, and academic functioning, as well as in their emotional and social well-being (Reference 2). Most children with SCD will require several hospitalizations because of severe pain crises, and almost 1 in 10 will have a sickle-related stroke (Reference 3).

Epidemiology and Nomenclature

Normal adult hemoglobin (HbA) is composed of two α-globin chains and two β-globin chains. Sickle hemoglobin (HbS) occurs when valine is substituted for glutamic acid at position 6 of the β-polypeptide chain. Hemoglobin C (HbC) is another genetic variant that occurs when lysine is substituted for glutamic acid as the sixth amino acid in the beta chain. Changes in the β-globin chain are primarily responsible for the sickling of the red blood cells (RBCs); however, the α-globin chain structure is identical in all forms (HbA, HbS, and HbC).

Sickle cell syndromes can be divided into two groups: SCD and sickle cell trait (SCT). Sickle cell trait is the heterozygous form of SCD in which the individual inherits one normal HbA gene and one HbS gene. Patients with SCT are usually asymptomatic or mildly symptomatic and are carriers of the sickle cell gene. Because *Plasmodium falciparum* cannot invade sickled RBCs easily, SCT is known to offer protection against clinical infections of malaria. Therefore, the sickle cell gene is more prevalent in tropical areas with a higher incidence of malaria. In the homozygous form of SCD (HbSS), also called *sickle cell anemia*, the patient inherits both abnormal genes, one from each parent. Compound heterozygous inheritance of HbS with

another mutation results in sickle cell hemoglobin C (HbSC) or one of two types of sickle cell β-thalassemia (HbS β^+thal and HbS β^0thal). Patients with HbSS and HbS β^0thal typically have a severer disease course than patients with other types because they do not have normal β-globin production (Reference 4).

Around 2 million people in the United States are carriers of the sickle cell gene. Most of them are of African ancestry, although those of Mediterranean and Middle Eastern descent may also have sickle cell mutations. More than 50,000 Americans have SCD, and for every 1 infant with SCD, 50 infants are identified as carriers. About 9% of African Americans carry the HbS gene. Homozygous HbS is the most common variant of SCD in the United States at 45%, followed by HbSC (25%), HbS β^+thal (8%), and HbS β^0thal (2%) (Reference 5).

Pathophysiology

In the fetus, fetal hemoglobin (HbF) is the predominant oxygen transport protein, and at birth, it constitutes 60% to 90% of RBC hemoglobin. Fetal hemoglobin contains two gamma chains instead of beta chains; therefore, RBCs with HbF do not sickle. Before birth, HbF undergoes a conversion from gamma chains to beta chains, and after the child is born, only a few RBC clones remain to produce HbF. Infants with SCD typically have few symptoms of the disease until their HbF concentrations fall, usually by age 6 months. In an adult, RBCs contain less than 1% HbF (Reference 6).

Because of high hemoglobin concentrations, RBCs are extremely flexible. Both HbA and HbS have the same solubility when they are oxygenated, and HbS will carry the oxygen normally. As oxygen is unloaded from the cell, HbS solubility decreases, leading to valine binding to sites on adjacent globin chains. The deoxygenated HbS will begin to form a gel-like substance that distorts RBCs into the classic crescent or sickle shape. When HbS is re-oxygenated, the RBC will resume its normal shape, but as this sickle/unsickle process is repeated, membrane damage occurs, and the cell loses its flexibility as well as its potassium and water. This leads to dehydrated, dense sickled cells that cannot resume their original shape and remain sickled, even when oxygenated. Vaso-occlusion will occur as the blood becomes more viscous and as sickled RBCs adhere to the vascular endothelium, blocking small blood vessels and resulting in local tissue hypoxia. A normal RBC will have a life span of 100–120 days. An irreversibly sickled RBC lives only 10–20 days, leading to anemia, which is common in patients with SCD (Reference 7).

In addition to the local tissue damage from vaso-occlusive crises, sickled cells may obstruct the spleen, leading to functional asplenia and splenomegaly. Patients with SCD are at an increased risk of infections from encapsulated bacteria (e.g., *Streptococcus pneumoniae*) because of this effect on the spleen. They may also have coagulation abnormalities because of decreased levels of protein C, protein S, and antithrombin III, as well as increased thrombin generation and platelet aggregation (References 8, 9).

Clinical Presentation and Diagnosis

Newborn Screening

Most infants with SCD appear healthy at birth and begin to exhibit symptoms only as their HbF concentrations decline during the first 6 months of life. Newer therapies and interventions have dramatically decreased morbidity in infants and children with SCD, so identifying these children before age 2 months is important. Neonatal screening for SCD is required in all 50 of the United States so that caregiver education can begin and care plans can be developed for these children. Screening is done by high-performance liquid chromatography or thin-layer isoelectric focusing, both of which have high sensitivity and specificity for SCT and SCD. All positive tests should be confirmed with a second test within 2 months. Because HbF is the primary hemoglobin in fetuses and the production of other hemoglobins (HbA, HgC, or HgS) does not occur until the last trimester of pregnancy, very premature neonates (those less than 28 weeks' gestation) may have false negatives (References 10, 11).

Signs and Symptoms

Children with SCT are typically asymptomatic, although girls may have more frequent urinary tract infections (Reference 12). Because of RBC sickling in the renal medulla, patients with SCT may be unable to maximally concentrate their urine, leading to an increased risk of dehydration. Although microscopic hematuria is rare, patients with SCT may exhibit gross hematuria after very high-intensity exercise (Reference 13).

The most common signs and symptoms of SCD are pain and anemia, and they usually manifest early in childhood. In children with HbS, anemia is seen within 6 months of birth. Anemia is chronic and hemolytic with hemoglobin concentrations between 7 g/dL and 10 g/dL. These children typically tolerate the anemia well. Anemia may be complicated by megaloblastic changes caused by folate deficiency. As HbS concentrations increase, pain episodes increase, usually together with fever. Splenomegaly is common during the first

year of life, together with functional asplenia. The spleen becomes fibrotic and eventually shrinks, leading to an increased risk of infection with encapsulated bacteria. A painful splenic sequestration crisis may occur, in which the spleen undergoes a sudden enlargement caused by the pooling of many sickled RBCs. Infants may also present with dactylitis, also known as hand-foot syndrome, a painful swelling of the hands and feet (References 4, 10, 12, 14). Clinical presentation of SCD in children may differ depending on the age at symptom onset. Infants and younger children may present with dactylitis, pneumococcal sepsis, meningitis, severe anemia, acute chest syndrome (ACS), pallor, jaundice, or splenomegaly. Older children may exhibit anemia, aplastic crisis, ACS, splenomegaly or splenic sequestration, cholelithiasis, and severe or recurrent abdominal or musculoskeletal pain (Reference 12). Children with HbSC usually have a less severe presentation, with less frequent pain episodes and a mild anemia in which the hemoglobin is greater than 9 g/dL. These children may also exhibit splenomegaly that will persist into adulthood (References 4, 12, 14).

Laboratory Diagnosis

Low hemoglobin counts (usually less than 10 g/dL) are common in patients with SCD. Red blood cell transfusions are not typically used unless hemoglobin falls below 7 g/dL and the patient is being treated for an acute complication such as ACS, a pain crisis, or an infection (Reference 12). Increased reticulocytes, platelets, and white blood cells are common findings in a complete blood cell count. Peripheral blood smears will show sickle cell forms (Reference 12).

Course and Prognosis of Disease

Growth and Development

Decreases in growth velocity and growth delays during puberty are commonly seen in children with SCD. Children and adolescents with SCD may also be below average for both height and weight, although this is independently associated with decreased hemoglobin concentrations, increased total energy expenditures, and nutritional intake (Reference 15). In adolescents, puberty is slow in onset, and delayed sexual maturation is common.

Morbidity and Mortality

Morbidity and mortality in SCD are caused by complications of the disease. In the past, 50% of patients with SCD did not survive to adulthood. Recent reports suggest that 85% of children with SCD will survive to age 18 years because of improvements in comprehensive care and early screening and intervention (Reference 12). Median survival is about 42 years for males and 48 years for females (Reference 12). Children younger than 3 years are more likely to die of infectious causes. Children who have dactylitis before age 1 year, severe anemia in the second year of life (hemoglobin concentrations less than 7 g/dL), and signs of leukocytosis without the presence of infection have higher morbidity and mortality. Morbidity and mortality in later years are secondary to chronic complications such as repeated pain crises, anemia, ACS, kidney dysfunction, and cerebrovascular complications, including stroke and lung disease (References 12, 16, 17).

Complications

Acute complications of SCD are unpredictable, and the rate and occurrence vary between patients. Because of functional asplenia, the risk of overwhelming sepsis from encapsulated microorganisms is high, especially from *S. pneumoniae*, *Haemophilus influenzae,* and *Salmonella* spp. Viral infections can also result in significant morbidity, especially from influenza and parvovirus B19 (References 12, 14, 18). By age 20, about 11% of patients with SCD will have had a stroke, with the highest incidence in children aged 2–5 years (Reference 19). Symptoms of stroke in children with SCD may include aphasia or dysphasia, hemiparesis, severe headache, cranial nerve palsy, seizures, stupor, and coma. Nonfocal signs, such as developmental delay and poor academic performance, may be indicative of ischemic central nervous system injury. The leading cause of death in patients with SCD is ACS. Any patient who shows a new infiltrate on chest radiography, together with symptoms of a lower respiratory tract infection and hypoxia, should be immediately treated. Acute chest syndrome may occur because of a patient's undergoing general anesthesia, during a patient's acute illness, or 2–3 days after a patient suffers a severe vaso-occlusive pain crisis. Early signs of ACS (e.g., cough, dyspnea, chest pain) should be immediately assessed and treated to prevent deterioration to respiratory failure. Priapism, a prolonged painful penile erection, is a common complication in males with SCD, occurring in 90% of males by age 18 years. Vaso-occlusive pain crises are the most common SCD crisis and are characterized by acute pain (often deep and throbbing) with tenderness, erythema, and swelling in the affected area. Recurrent acute pain crises can lead to bone, joint, and organ damage, as well as chronic pain. These acute crises may be precipitated by infection, dehydration, extreme changes in weather, and stress (References 12, 14). Aplastic crisis, usually caused by infection with parvovirus B19, occurs when there is a decrease in hemoglobin with an acute, rapid decrease in the patient's reticulocyte count, usually to less than 1% (Reference 12). Patients in acute aplastic crisis may present with severe pain, ACS, and splenic

sequestration. Splenic sequestration in young children may lead to an acutely enlarged spleen, together with a rapid drop in the patient's hemoglobin concentration leading to hypovolemia, shock, and death.

Chronic complications generally are a result of organ damage, affecting the heart, lung, brain, bones and joints, eyes, kidneys, and gallbladder. Although much more common in adult patients with SCD, children and adolescents with poorly managed disease or severe repeated acute complications may also begin to show these chronic complications (Table 1).

Treatment

Therapy Goals

The therapy goals for children and adolescents with SCD are to decrease complications and morbidity to improve quality of life. This requires a comprehensive multidisciplinary approach including medication, regular examinations, education of both patients and caregivers, and psychosocial support (Reference 12). Preteens and adolescents should be actively involved in the management of their disease. Medications are aimed at maintaining health through prophylactic measures and treating acute complications and crises as they arise.

Preventive Therapy

Immunizations

All children with SCD should receive all routine immunizations recommended by the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention and the American Academy of Pediatrics (see Pediatric Vaccines chapter). The impaired splenic function that develops in these children during childhood increases the risk of infection with encapsulated bacteria (e.g., *S. pneumoniae*, *H. influenzae*, *Salmonella* spp.). Children with SCD are up to 600 times more likely to suffer from invasive pneumococcal disease, especially if they are younger than 2 years (Reference 21). Vaccination with 13-valent pneumococcal vaccine and *H. influenza* vaccine is crucial in this population, and it has significantly decreased morbidity and mortality in children younger than 2 years with SCD. Despite appropriate vaccination, some children with SCD will still have high rates of invasive pneumococcal disease. The 23-valent polysaccharide vaccine contains the most common pneumococcal isolates seen in older children and adults. All children older than 2 years should also receive the 23-valent vaccine, with the first dose separated from the last dose of the 13-valent vaccine by at least 2 months. A second dose of the 23-valent vaccine is recommended 5 years after the initial dose. In addition to pneumococcal vaccine, children with SCD older than 2 years who are scheduled for surgical splenectomy or who have functional asplenia should receive meningococcal vaccine. When the first dose of meningococcal vaccine is administered between age 2 and 6 years, a second dose of meningococcal conjugate vaccine is recommended 3 years after the initial dose (Reference 22).

Penicillin Prophylaxis

Despite appropriate vaccination against pneumococcal disease, available vaccines do not cover all serotypes of *S. pneumoniae*. The use of prophylactic penicillin has dramatically decreased mortality from invasive

Table 1. Systems Affected by Those with Sickle Cell Disease (References 4, 10, 12, 14, 20)

System	Complication
Cardiovascular	Myocardial infarction, anemia
Gastrointestinal	Acute hepatic ischemia, cholestasis, acute or chronic cholelithiasis, acute or chronic liver disease (caused by drug toxicity or hepatitis C contracted from transfusions)
Genitourinary	Priapism, infertility
Musculoskeletal	Acute pain crises, vaso-occlusive pain crises, chronic pain, bone infarcts, osteonecrosis, dactylitis, osteomyelitis, septic arthritis, growth delays
Neurologic	Transient ischemic attacks, silent ischemic lesions, stroke, neurocognitive compromise
Ocular	Eye vessel occlusion, proliferative sickle retinopathy
Pulmonary	Acute chest syndrome, hypoxemia
Renal	Hematuria, proteinuria, renal infarct, focal segmental glomerulosclerosis, renal medullary carcinoma, enuresis
Skin	Leg ulcers
Other	Delayed puberty, splenomegaly, infectious complications secondary to *H. influenza*, *S. pneumoniae*, *Salmonella*, leukocytosis

pneumococcal infections in young children (Reference 12). All children with SCD should be initiated on prophylactic penicillin at age 2 months and continued until at least 5 years old (Reference 12). Penicillin V potassium 125 mg orally twice daily is given until age 3; then, the dose is increased to 250 mg orally twice daily until the child is at least 5 years old. Benzathine penicillin 600,000 units intramuscularly every 4 weeks beginning at age 6 months and continued to age 6 years is an option when adherence to the oral regimen is a concern. Penicillin-allergic children can receive erythromycin orally at 10 mg/kg twice daily (References 12, 14). Some children will develop invasive pneumococcal infections despite use of prophylactic penicillin. Penicillin prophylaxis should be continued indefinitely in any child who has a history of severe invasive pneumococcal infections and in those with functional or surgical asplenia. In these patients, the dose remains 250 mg orally twice daily (References 12, 14).

Folic Acid Supplementation

Folic acid supplementation is generally recommended in children with SCD who have chronic hemolysis. Infants should receive 0.1 mg orally once daily, and children aged 1–4 years should receive 0.3 mg orally once daily. Children older than 4 years and adolescents should receive 0.4–1 mg orally once daily (Reference 23).

Hydroxyurea

Hydroxyurea is a ribonucleotide reductase inhibitor that prevents DNA synthesis, increases HbF production, and decreases neutrophils in patients with SCD. It has also been shown to decrease RBC adhesion to the intravascular endothelium and increase concentrations of nitric oxide, which is a regulator involved in physiologic disturbances. Landmark studies in adults with SCD who received hydroxyurea showed a reduction in pain crises, hospitalization rates, RBC transfusions, ACS incidence, and mortality. The HbF concentrations increased, and hemolysis decreased (References 24, 25). Studies in children and adolescents with SCD have shown results similar to those found in the adult hydroxyurea trials, with no adverse affects on growth and development (References 12, 26, 27).

Hydroxyurea treatment should be considered in children and adolescents with SCD who have a history of frequent vaso-occlusive crises, severe symptomatic anemia, repeated history of ACS, or other history of severe vaso-occlusive complications (Reference 12). Hydroxyurea can be used in children as young as 6 months. The therapy goals with hydroxyurea are to reduce the number and severity of acute SCD complications, including pain crises, and to improve the patient's quality of life. Hydroxyurea dosing should be individualized on the basis of the patient's HbF concentration and hematologic response. For children with SCD, initiate hydroxyurea at 15 mg/kg orally once daily, and increase in increments of 5 mg/kg every 12 weeks to a maximum dose of 35 mg/kg/day. Complete blood cell counts should be evaluated every 2 weeks during dose titration and then every 4–6 weeks once the dose is stabilized (Reference 28).

Children and adolescents receiving hydroxyurea should be closely monitored for both safety and efficacy. Mean corpuscular volume will increase as the concentration of HbF increases. If the mean corpuscular volume does not increase with hydroxyurea use, patients' bone marrow may be unable to respond, the dose may be inadequate, or patients may not be adherent to their therapy. Response to therapy can also be assessed by monitoring the HbF concentrations, which should increase 15% to 20%.

Although hydroxyurea is only commercially available in a solid oral dosage form as 200-, 300-, 400-, and 500-mg capsules, an extemporaneous suspension can be compounded for younger children. Patients on solid dosage forms should have their dose rounded to the nearest available capsule or combination of capsules. The most common adverse effect of hydroxyurea is mild to moderate neutropenia, and other reported effects include mild thrombocytopenia, severe anemia, rash, nail changes, and headaches. All adverse effects are reversible upon discontinuation of the product. If the hemoglobin concentration is less than 5 g/dL, the absolute neutrophil count is less than 2,000/mm^3, or the reticulocyte count is less than 80,000/mm^3 when the hemoglobin concentration is less than 9 g/dL, then hydroxyurea should be discontinued until recovery of one or more of the cell counts. After recovery, hydroxyurea should be reinitiated at a daily dose 2.5 mg/kg less than the dose at which toxicity occurred. Hydroxyurea should then be titrated by 2.5 mg/kg every 12 weeks (References 28, 29). Hydroxyurea is teratogenic in high doses in animal studies, so female patients should be counseled to use effective contraception. Studies are evaluating hydroxyurea use in children with SCD who have suffered a stroke to reduce the need for chronic RBC transfusions and prevent end-organ damage in young children with SCD.

Transfusion Therapy

Transfusions are indicated in children and adolescents with SCD for acute exacerbations of anemia that require supplemental oxygen, acute severe vaso-occlusive crises including stroke, ACS, and acute multiorgan failure and in patients who are preparing for surgery involving general anesthesia or radiologic procedures requiring the use of ionic contrast. Hyperviscosity may occur if the hemoglobin concentration is increased to greater than 10–11 g/dL. Volume overload is a concern if the anemia is corrected too rapidly, which may lead to congestive heart failure (Reference 12).

Studies have shown that in children, the use of chronic RBC transfusions decreases stroke recurrence from 50% to 10% over 3 years (Reference 30). In addition, chronic transfusions are used in children and adolescents to reduce certain SCD complications such as vaso-occlusive pain crises and ACS. Without chronic transfusion therapy, up to 93% of children with SCD who have had a stroke will suffer a recurrence. Several transfusion methods have been used, including simple transfusion, exchange transfusion, and erythrocytapheresis. The goal of chronic transfusion therapy is to reduce erythropoiesis and maintain the HbS concentration at less than 30% of the total hemoglobin concentration (Reference 12). Depending on the HbS concentrations, transfusions are administered every 3–4 weeks. For secondary stroke prevention, studies have indicated that lifelong transfusions are required; stroke risk increases once the transfusions are discontinued (Reference 12). Children and adolescents who should be considered for chronic transfusion therapy are those with severe or recurrent ACS, recurrent priapism, debilitating chronic pain, chronic organ failure, transient ischemic attacks, abnormal transcranial Doppler studies, and intractable leg ulcers, as well as those with severe chronic anemia who also have heart failure.

Risks associated with transfusions include alloimmunization, hyperviscosity, viral transmission, volume overload, transfusion reactions, and iron overload. Alloimmunization can be minimized with leukocyte-reduced RBCs or human leukocyte antigen (HLA)-matched units. Although the risk of viral transmission through transfusion is low, all patients with SCD should be immunized against hepatitis B and should be monitored for hepatitis C and other bloodborne pathogens. Parvovirus is associated with aplastic crisis and may be present in 1 of every 40,000 units of RBCs. Sickle cell hemolytic transfusion reaction syndrome is a unique condition that occurs because of alloimmunization and may lead to acute or delayed transfusion reactions. Symptoms of hemolytic transfusion reaction syndrome mimic pain crises. Delayed reactions will occur 5–20 days post-transfusion. Severe anemia may occur after the transfusion because of a rapid decrease in hemoglobin and hematocrit with suppression of erythropoiesis. Additional transfusions may worsen the clinical picture because of the presence of autoimmune antibodies. Recovery will occur only after all transfusions are discontinued and will be evidenced by a gradual increase in hemoglobin and reticulocytes (References 12, 22, 31).

Iron Chelation

Iron overload is a concern in any patient maintained on chronic transfusions for more than 1 year because humans do not have an effective means to excrete excess iron (Reference 32, 33). There is no consensus on the best way to estimate iron overload in children with SCD maintained on chronic transfusion therapy. Most comprehensive sickle cell centers in the United States use a combination of serum ferritin concentrations, cumulative RBC transfusion volumes, and liver biopsy to determine the patient's iron status. Each milliliter of packed RBCs contains about 1 mg of elemental iron. Chelation therapy should be considered when the child or adolescent has received a cumulative total of 120 mL/kg of RBCs (around 20 units) and/or when the serum ferritin concentration is greater than 1,500–2,000 ng/mL (References 12, 33). If a liver biopsy is completed, chelation should start when the liver tissue iron content is greater than 7 mg per gram of dry tissue weight (Reference 34).

Two drugs are used in the United States for iron chelation in pediatric patients, deferoxamine and deferasirox (Table 2). Deferoxamine is a parenteral iron chelator that complexes with trivalent ferric ions to form ferrioxamine, which is then removed by the kidneys. Its poor oral bioavailability and short half-life necessitate an 8- to 12-hour subcutaneous infusion. Patients receiving deferoxamine should also receive supplemental ascorbic acid starting 1 month after deferoxamine initiation. Ascorbic acid increases the availability of iron for chelation. Children with preexisting cardiac conditions should not receive supplemental ascorbic acid. Contraindications include those with renal impairment. Complications of deferoxamine therapy may include ototoxicity, allergic reactions, growth failure, ocular disturbances, pulmonary hypersensitivity, and arthralgias. Adherence to deferoxamine can be an issue because of its route of administration. Children and adolescents receiving chelation with deferoxamine should have regular eye and auditory examinations. Deferasirox is an oral iron chelator that selectively binds iron, forming complexes that are excreted through the feces. It is available in an orally dispersible tablet that should be dissolved in water, orange juice, or apple juice, and it should be consumed 30 minutes before eating. Deferasirox is U.S. Food and Drug Administration (FDA) labeled for use in children 2 years and older. Serum ferritin concentrations should be monitored closely in patients receiving deferasirox. If serum ferritin decreases to less than 500 ng/mL, deferasirox should be discontinued and then reinitiated once the serum ferritin level increases to 500 ng/mL or higher (Reference 29). Adverse effects include headache, rash, abdominal pain, nausea, diarrhea, arthralgia, increased serum hepatic transaminases and creatinine, and visual and auditory disturbances. As with deferoxamine, regular annual eye and auditory examinations are recommended. Doses of deferasirox should be decreased if the patient's serum creatinine increases above the age-appropriate upper limit of normal on two consecutive measurements. If the patient's serum creatinine increases

Table 2. Iron Chelators Used in Children with SCD and Iron Overload

Drug	Route	Dosage Regimen	Toxicities	Notes
Deferoxamine	SC	▪ 20–50 mg/kg/day for 4–7 days/week ▪ Maximal dose: 2 g/day ▪ Infuse over 8–12 hours	▪ Ototoxicity ▪ Visual impairment ▪ Arthralgia ▪ Headache ▪ ARDS ▪ Hypersensitivity	▪ Supplement with oral ascorbic acid 50–150 mg/day.[a] ▪ Do not use in severe kidney dysfunction.
Deferasirox	Oral	▪ 20 mg/kg once daily ▪ Titrate every 3–6 months by 5–10 mg/kg/day ▪ Maximal dose: 40 mg/kg/day ▪ Round to available whole-tablet dose: 125, 250, 500 mg	▪ Headache ▪ Rash ▪ Abdominal pain ▪ Nausea ▪ Arthralgia ▪ Visual impairment ▪ Increased hepatic transaminases ▪ Increased SCr	▪ Disperse tablet in water or orange or apple juice before administration. ▪ Adjust dose in kidney dysfunction.

[a]Do not use supplemental ascorbic acid in patients with preexisting cardiac conditions.
ARDS = acute respiratory distress syndrome; SC = subcutaneous; SCD = sickle cell disease; SCr = serum creatinine.
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to more than 2 times the upper limit of normal for age, or the creatinine clearance is less than 40 mL/minute, deferasirox should be discontinued until measurements return to baseline (References 25, 26, 33).

Deferiprone was recently approved by the FDA for treatment of transfusional iron overload in adults with thalassemia syndromes who have inadequate responses to other chelation therapies. Deferiprone binds to ferric ions and forms a complex, which is excreted in the urine. It is an oral agent administered three times/day. Agranulocytosis has been reported in patients receiving deferiprone; therefore, careful monitoring is necessary. Studies of deferiprone use in children are limited.

Acute Complication Management

Infection and Fever

All children with SCD with a temperature of 101.3°F (38.5°C) or higher should seek immediate medical attention because the condition of these children may deteriorate rapidly. Because of splenic dysfunction, children with SCD are at high risk of complications from encapsulated bacteria such as *S. pneumoniae*. Hospital admission may be necessary, especially in infants younger than 1 year, patients with elevated white blood cell counts, patients with a history of sepsis or bacteremia, or any patient who appears acutely ill. Physical examination, blood cultures, complete blood cell counts including reticulocyte count, and chest radiographs if cough is present or if the child has difficulty breathing should be completed. Patients should be immediately initiated on empiric broad-spectrum intravenous antibiotics such as cefotaxime, ceftriaxone, or cefuroxime. Patients who have a true allergy to cephalosporins may be treated with clindamycin. Vancomycin should be initiated if the patient has a history of a staphylococcal infection or is severely ill. If mycoplasma pneumonia is suspected, a macrolide such as azithromycin may be initiated. Pain and swelling in an extremity may indicate bone infarct, and osteomyelitis should be considered. *Salmonella* spp. are the most common cause of osteomyelitis in this population, followed by *Staphylococcus aureus* (Reference 12). Prophylactic penicillin regimens should be held while the patient is receiving broad-spectrum antibiotics. Intravenous fluids to prevent dehydration may also be indicated, as well as treatment of fever with appropriate doses of ibuprofen or acetaminophen (References 4, 10, 14).

Acute Chest Syndrome

Patients with ACS will require hospitalization because they may rapidly deteriorate into respiratory failure and death. Acute chest syndrome may present during an acute illness or 2–3 days after a severe vaso-occlusive pain crisis. A patient receives a diagnosis of ACS when a new infiltrate is detected on chest radiograph, together with symptoms of a lower respiratory infection and possibly hypoxemia (Reference 12). Acute chest

syndrome may be caused by a viral or bacterial infection, pulmonary infarct, and pulmonary fat emboli. Gram-negative, gram-positive, and atypical bacteria should be suspected, and early use of appropriate empiric parenteral antibiotics such as a cephalosporin and a macrolide is important. Oxygen therapy may be indicated if the patient is hypoxic or in respiratory distress. Oxygen saturations measured with pulse oximetry should be maintained at 92% or above. Intravenous fluid use should be monitored closely to avoid fluid overload, which may lead to pulmonary edema and increase respiratory distress. Patients may require transfusion with RBCs, depending on their hemoglobin concentration, to improve oxygenation. Incentive spirometry is encouraged every 2 hours to help prevent atelectasis and to help with lung expansion. Appropriate management of pain is crucial, but care should be taken to prevent opioid-induced hypoventilation. Corticosteroid use is controversial because it has been associated with higher complication rates and readmission (References 12, 35–38).

Cerebrovascular Accidents

Initial assessment of stroke in a child with SCD should include a physical examination, a complete blood cell count including reticulocyte count, and noncontrast computer tomography or magnetic resonance imaging. Close monitoring every 2 hours with both physical and neurologic examinations is recommended. Treatment may include transfusion to maintain a hemoglobin concentration at 10 g/dL and an HbS concentration at less than 30%. Patients who seize may require anticonvulsants, and interventions may be needed to decrease intracranial pressure. Children with a history of stroke should be initiated on chronic transfusion therapy (Reference 12). The use of clopidogrel and other antiplatelet agents has not been studied in children with SCD and is not recommended.

Screening for early detection of ischemic events with transcranial Doppler ultrasonography is recommended for all children with SCD beginning at age 2 years, and screening should be performed on an annual basis. In the STOP (Stroke Prevention Trial in Sickle Cell Anemia) study, screening followed by chronic transfusion therapy significantly reduced the incidence of primary stroke (Reference 39). Children with positive findings may be candidates for chronic transfusion therapy for primary stroke prevention (References 40, 41).

Priapism

Two types of priapism are seen in children and adolescents with SCD. Stuttering episodes last from a few minutes to less than 2 hours, and they recur and resolve spontaneously. Severe episodes may last longer than 2–4 hours and will require medical attention to prevent complications that may lead to impotence. Therapy goals for priapism are to provide pain relief, provide detumescence, and preserve fertility. Patients can self-treat initially by increasing oral fluid intake, urinating, taking warm baths, and using analgesics. If the episode continues for more than 2 hours, patients should be instructed to seek medical attention.

Initial treatment of severe prolonged episodes should include intravenous fluids and analgesics. Patients may require RBC transfusion if their hemoglobin concentration is below their baseline. Both vasodilators and vasoconstrictors have been used to treat severe episodes. Aspiration of penile blood, followed by intracavernous irrigation with epinephrine (1:1,000,000), has been used effectively with minimal complications (References 42, 43).

Several medications have been used to prevent or decrease episodes of priapism. First-line therapy is pseudoephedrine 30–60 mg orally at bedtime. Terbutaline 5 mg orally at bedtime has been used, but the evidence is not consistent. In severe cases, initiating the patient on hydroxyurea or chronic transfusion therapy may be beneficial (References 12, 42).

Crisis Management

Aplastic Crisis

Treatment of aplastic crisis is generally supportive because most patients will spontaneously recover. Patients may require pain management and transfusion if the anemia is severe or if they are symptomatic. The most common cause of aplastic crisis is infection with human parvovirus B19. Patients should be isolated from immunocompromised individuals and pregnant women because parvovirus is highly contagious (References 4, 10, 12).

Sequestration Crisis

In young children, splenic sequestration of RBCs can lead to a rapid drop in the patient's hemoglobin concentration and an acutely enlarged spleen. This shift can result in hypovolemia, shock, and death. Treatment should include RBC transfusions to correct the hypovolemia and broad-spectrum antibiotics because infections can precipitate the sequestration crisis (References 4, 12). Management of recurrent episodes involves chronic RBC transfusions and splenectomy. Splenectomy is usually delayed in children until after age 2 years because of the risk of postsplenectomy septicemia (References 12, 14).

Vaso-occlusive Pain Crisis

Most cases of mild to moderate pain in children and adolescents with SCD can be managed at home. Patients should be instructed to increase their oral fluid intake, rest, apply warm compresses to the painful areas,

and take oral analgesics such as acetaminophen or ibuprofen with or without an opioid (codeine or hydrocodone). In moderate to severe cases, the patient should be hospitalized for treatment. Intravenous or oral fluids at 1.5 times maintenance should be initiated, with careful monitoring to prevent fluid overload (Reference 12). Transfusion may be required in patients who are anemic to bring their hemoglobin concentration back to their baseline level. Any patient presenting with fever should be initiated on broad-spectrum antibiotics empirically because infection may lead to a pain crisis. Aggressive pain management is required and should be individualized and titrated to achieve the best response in the patient (Table 3). Pain control should be assessed on a regular basis with a self-reported pain scale. Patients receiving intravenous opioids should be encouraged to use incentive spirometry to prevent atelectasis. Nausea and vomiting are common adverse effects of the opioid analgesics and can be managed with antiemetics such as promethazine or ondansetron. Promethazine is contraindicated in children younger than 2 years, and it should be used with caution in young children because of the increased risk of respiratory depression. All patients receiving opioids should be assessed for stool frequency and initiated on prophylactic stool softeners and stimulant laxatives. Pruritus can be severe in patients taking higher doses of opioids, and use of an antihistamine such as diphenhydramine on a scheduled routine may be necessary. The use of low-dose continuous infusion of naloxone may be helpful when other agents do not adequately relieve pruritus (Reference 44).

Hematopoietic Stem Cell Transplantation

The only cure for SCD is a hematopoietic stem cell transplantation using marrow from a donor who does not have SCD, usually an HLA-matched sibling. More than 250 patients with SCD have received transplants

Table 3. Drug Regimens for Vaso-occlusive Pain Crises in Children with SCD

Mild to Moderate Pain	Acetaminophen with codeine: 1 mg/kg (based on codeine) PO every 6 hours
	Hydrocodone with acetaminophen: 0.2 mg/kg (based on hydrocodone) PO every 6 hours
	Ibuprofen: 10 mg/kg PO every 6–8 hours[a]
	Naproxen: 5 mg/kg PO every 12 hours[a]
Severe Pain	Morphine:
	Intermittent doses: 0.05–0.15 mg/kg IV every 3–4 hours
	CI: 0.02–0.05 mg/kg/hour; titrate to effect
	PCA: 0.02–0.03 mg/kg/hour basal + 0.02–0.06 mg/kg IV every 10 minutes
	Hydromorphone:
	Intermittent doses: 0.005–0.015 mg/kg IV every 3–4 hours
	CI: 0.003–0.005 mg/kg/hour IV; titrate to effect
	PCA: 0.003–0.005 mg/kg/hour basal + 0.003–0.005 mg/kg IV every 10 minutes
	Ketorolac: 0.5 mg/kg up to 30 mg per dose IV every 6 hours[a,b,d]
Adjunctive Treatment	Docusate: 5 mg/kg/day PO divided in one to four doses
	Diphenhydramine: 1 mg/kg/dose IV/PO every 6 hours
	Naloxone (for itching): 0.25–1 mcg/kg/hour IV infusion
	Promethazine: 0.25 mg/kg IV/PO every 6 hours (maximal dose: 25 mg)[c]
	Ondansetron: 0.15 mg/kg/dose IV/PO every 8 hours

[a]Use with caution in patients with kidney failure, dehydration, or bleeding.
[b]Use in children aged 1 year and older. Use with caution in children aged 6–12 months.
[c]Contraindicated in children younger than 2 years because of potential for severe and potentially fatal respiratory depression.
[d]Limit use to 5 days maximum.
CI = continuous infusion; IV = intravenously; PCA = patient-controlled analgesia; PO = orally (by mouth); SCD = sickle cell disease.
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from an HLA-identical sibling (Reference 45). Ideal SCD transplant recipients are younger than 16 years, with an HLA-identical donor and at least one of the following:

- Stroke,
- ACS,
- Recurrent severe pain episodes,
- Impaired neurologic function with an abnormal magnetic resonance imaging scan,
- Mild to moderate chronic sickle lung disease,
- Sickle nephropathy,
- Bilateral proliferative retinopathy,
- Osteonecrosis of several joints, or
- RBC alloimmunization secondary to long-term transfusion treatment (References 12, 45)

Less than 1% of children with SCD have an HLA-identical sibling who does not have SCD, which is the main barrier to the use of transplantation in SCD.

Conclusions

Caring for children with SCD requires a comprehensive, multidisciplinary approach to prevent long-term complications and to improve or maintain the patient's quality of life. Children with SCD should have regularly scheduled assessments and treatment plans available for what to do if fever, pain, or symptoms of infection occur. The education of both the patient and the caregivers should be routinely updated.

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CHAPTER 51

Childhood Acute Lymphoblastic Leukemia

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Learning Objectives

1. Describe the impact of acute lymphoblastic leukemia (ALL) on the pediatric population.
2. Discuss the typical clinical presentation and diagnostic evaluation for a child with ALL.
3. Recognize major prognostic factors in pediatric patients with ALL.
4. Summarize the typical treatment approach for a patient with newly diagnosed ALL, including the phases of therapy and pharmacologic agents used in management.
5. Give an example of a subgroup of patients with ALL having different therapeutic considerations and approaches to management.
6. List acute and long-term toxicities from therapy for ALL.

Abbreviations in This Chapter

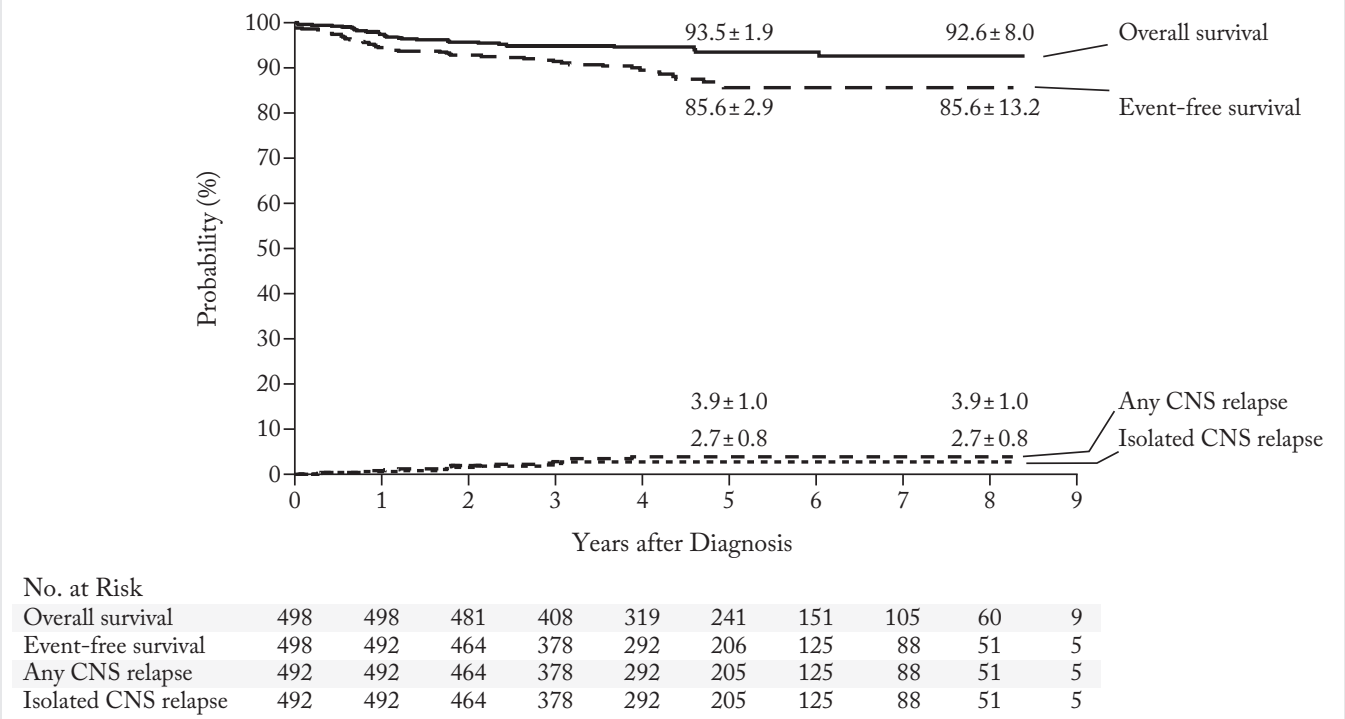
ALL	Acute lymphoblastic leukemia
EFS	Event-free survival
GCSF	Granulocyte colony-stimulating factor
HSCT	Hematopoietic stem cell transplantation
MRD	Minimal residual disease
Ph	Philadelphia chromosome
TLS	Tumor lysis syndrome
TPMT	Thiopurine methyltransferase

Introduction

Acute lymphoblastic leukemia (ALL) is the most frequent malignancy occurring during childhood and is responsible for about 75% of all childhood leukemias, resulting in an annual incidence of 30–40 new cases per 1 million children in the United States (References 1, 2). Survival has drastically improved, partly because of a better understanding of the biology of the disease as well as by the therapeutic advances made through clinical trials, illustrated by improvements in 5-year survival rates from around 55% in the 1970s to 85% to 90% in the most recently reported period of 1999–2006. Figure 1 is an example of survival outcomes from a recently conducted clinical trial of patients with newly diagnosed ALL (References 2–5). Although ALL can occur anytime during childhood development, presentation usually occurs between 2 and 5 years of age (Figure 2) (References 6, 7). In the United States, childhood ALL occurs with the highest incidence in Hispanic children, followed by whites and African Americans (References 8, 9). The incidence of ALL is higher in boys than in girls, and boys tend to present with more high-risk features than girls (References 8, 10).

Although the exact factors leading to the development of ALL remain unknown, much research has been done to investigate risk factors that may contribute to its development. However, the contribution of these risk factors remains controversial because many of the trials have produced conflicting results. From the environmental perspective, exposure to ionizing radiation has been linked with the development of ALL or acute myelogenous leukemia (Reference 11). Potential sources of ionizing radiation include nuclear accidents or atomic bombs and diagnostic x-rays, as well as living near a nuclear facility. Other environmental factors studied include exposure to electromagnetic fields, cigarette smoke, hydrocarbons, and pesticides (References 8, 11–13). Certain genetic factors can increase a child's likelihood of developing ALL. There is a high leukemia concordance rate in identical twins, and there are increased rates of leukemia in siblings of patients with childhood ALL (References 8, 11). In addition, children with other types of inherited diseases such as Fanconi anemia, ataxia telangiectasia, Down syndrome, and neurofibromatosis are at an increased risk of developing ALL (References 8, 11). Other factors that have been investigated as potentially contributing to the development of ALL include lack of exposure to infections, increased maternal and/or paternal age, increased birth weight, maternal alcohol exposure, household radon exposure, and chemical contamination of groundwater (References 8, 14, 15). These potential contributing factors must be interpreted with caution because reports are conflicting regarding their importance.

To better understand the pathogenesis of ALL, it is essential to understand the normal hematopoietic process. In brief, hematopoiesis begins with a pluripotent stem cell that is capable of differentiating into myeloid and lymphoid stem cells. The lymphoid progenitor cell then further differentiates into T and B lymphocytes. In the development of ALL, the lymphoid progenitor cell is defective in some way such that it does not undergo terminal differentiation, leading to uncontrolled



No. at Risk

Overall survival	498	498	481	408	319	241	151	105	60	9
Event-free survival	498	492	464	378	292	206	125	88	51	5
Any CNS relapse	492	492	464	378	292	205	125	88	51	5
Isolated CNS relapse	492	492	464	378	292	205	125	88	51	5

Figure 1. Kaplan–Meier and Kalbfleisch and Prentice Analyses of Outcomes in Children with Acute Lymphoblastic Leukemia. The overall survival, event-free survival, cumulative risk of any central nervous system (CNS) relapse (combined plus isolated), and cumulative risk of isolated CNS relapse are shown. The plus–minus values for 5-year and 8-year rates are means ±SE.

Pui CH, Campana D, Pei D, Bowman WP, Sandlund JT, Kaste SC, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 2009;360:2730–41 (Reference 5). Copyright 2009, with permission from the Massachusetts Medical Society.

proliferation of immature lymphoblasts in the bone marrow (References 16, 17). This uncontrolled proliferation results in expanded populations of leukemia blast cells (lymphoblasts), which in turn can cause a decrease in normal hematopoiesis, leading to signs of bone marrow failure. The lymphoblasts can be either T or B lymphocytes, which is determined by analyzing the antigen expression on the surface of the lymphoblasts. Identification of the lineage involved is important for appropriate therapy decisions, risk stratification, and prognostic implications (Reference 18).

Clinical Presentation and Diagnostic Evaluation

The clinical presentation of a child with ALL varies depending on the duration of symptoms and the degree of involvement of the bone marrow and other sites. Common symptoms that may be reported on presentation include bone pain, pallor, bruising, fatigue, weight loss, fever, and potentially an enlargement of the liver, lymph nodes, and spleen (Reference 6). These symptoms occur because of the effects of the leukemia on normal hematopoietic function and because the leukemia blasts can infiltrate organs. A thorough physical examination should be completed to identify objective findings of ALL, including a testicular examination for males.

Once a patient has been identified with signs and symptoms suggestive of leukemia, it is imperative that a thorough laboratory analysis be conducted in a timely fashion. A complete blood cell count will often show decreased hemoglobin and hematocrit, decreased platelet counts, and a white blood cell (WBC) count that may be normal, elevated, or low. The differential on the WBC count will sometimes show the presence of blast cells, which corresponds to the absolute neutrophil count being low because normal hematopoietic function is compromised. The peripheral blood smear can be sent for morphologic analysis to identify the presence of leukemic blast cells. Care must be used in interpreting the presence of blasts on the peripheral blood smear because other causes may exist for the presence of these immature cells, such as a viral infection (Reference 19). In addition, a comprehensive metabolic panel and uric acid should be obtained to check the patient's renal function and look for the presence of electrolyte abnormalities that may be suggestive of tumor lysis syndrome

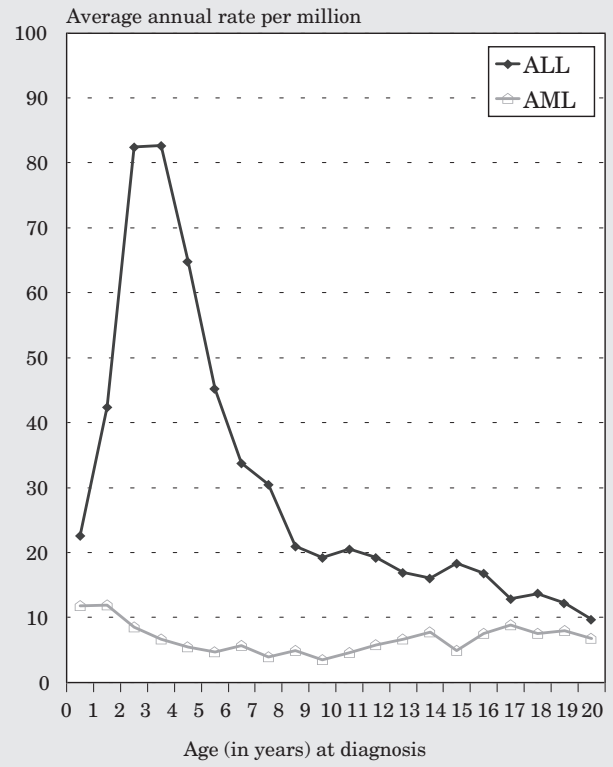


Figure 2. Age-specific incidence rate, United States SEER Program, 1986–1994 (Reference 7).

(TLS). Tumor lysis syndrome will be discussed in more detail in the supportive care section of this chapter. Because the signs, symptoms, and clinical presentation of childhood leukemia are often nonspecific, it is important to include other disease states in the differential diagnosis. Nonmalignant diseases that might have similar presenting features include, but are not limited to, juvenile rheumatoid arthritis, infectious mononucleosis, osteomyelitis, aplastic anemia, and idiopathic thrombocytopenic purpura (Reference 19).

Next in the diagnostic evaluation is to obtain a bone marrow aspirate and/or biopsy to confirm the suspicion for ALL. At the same time, a diagnostic lumbar puncture is performed to evaluate central nervous system (CNS) involvement (Reference 6). Intrathecal chemotherapy may be given during the diagnostic lumbar puncture if the diagnosis of ALL has already been confirmed on the basis of peripheral blood analysis. The specimens obtained during these procedures are analyzed by various techniques including flow cytometry, immunophenotyping, and cytogenetic studies. These techniques are used to identify leukemic blasts, determine the extent of involvement, and learn more specific details about the leukemia such as antigen expression and cytogenetic abnormalities (Reference 6). These test results are important to determine the prognosis and to stratify the patient's therapy on the basis of risk of relapse.

Classification

Childhood ALL can be classified on the basis of morphology, immunophenotype, and cytogenetic abnormalities. The French-American-British (FAB) system was used in the past to categorize ALL into three categories, L1, L2, and L3, based on cytologic features of the lymphoblast in the bone marrow biopsy specimen (Reference 8). The FAB system is no longer used to classify leukemia because it does not correlate well with risk stratification, and there are now more advanced and more accurate methods for classification (References 8, 20). Immunophenotyping is one such method that uses antigens and other markers expressed on the cell surface to categorize the subtype of ALL (Reference 8). Bone marrow samples are analyzed for cytogenetic abnormalities to better assess risk factors and prognosis, the details of which will be discussed further in the next section (Reference 8).

Prognostic Factors

Throughout decades of clinical trials, a great deal of knowledge has been gained about different features that a patient may or may not have and the effect of these factors on outcomes. These factors affect treatment decisions such that more intensive therapy is provided to patients with poor prognostic features to maximize outcomes, whereas therapy is often minimized for patients with favorable features to eliminate excessive toxicity in the subset of patients likely to have good long-term survival (Reference 21). Table 1 provides an overview of some of the main prognostic factors, both favorable and unfavorable.

Age and WBC count at diagnosis are two strong prognostic factors that will help determine the initial therapy the patient will receive during induction. Infants (younger than 1 year at diagnosis) and children 10 years and older are at a higher risk of relapse and will receive more intensive therapy to overcome this high-risk factor (References 6, 21, 22). A presenting WBC count of 50,000/μL or more has been associated with a poor outcome, so these patients will also be considered high risk and receive more intensive therapy (References 6, 21, 22).

Chromosomal abnormalities in the leukemic blast cell have prognostic importance. Before discussing some of the specific abnormalities with prognostic significance, it is important to have a basic understanding of the terminology and nomenclature used. There are two main types of chromosomal abnormalities: changes in the number of chromosomes (gains and losses) and structural changes (translocations, insertions, inversions, and deletions) (Reference 23). A translocation occurs when genetic material is rearranged between chromosomes. An example of a translocation would be t(9;22)(q34;q11), which identifies the presence of the Philadelphia

Table 1. Favorable and Unfavorable Prognostic Factors in Childhood ALL

Factor	Favorable Prognostic Factors and Their Approximate Incidence (%)	Unfavorable or Less Favorable Prognostic Factors and Their Approximate Incidence (%)
Age at diagnosis	≥1 and <10 years (77%)	<1 year (3%) or ≥10 years (20%)
Gender	Female (45%)	Male (55%)
White blood cell count at diagnosis	<50,000/μL (80%)	≥50,000/μL (20%)
Immunophenotype	$CD10^+$ precursor B-cell ALL (83%)	$CD10^-$ precursor B-cell ALL (4%), T-ALL (13%)
CNS disease[a]	CNS 1 (80%)	CNS 3 (3%), TLP+ (7%)
Genetic features[b]	Hyperdiploidy (20%), TEL/AML1 positivity (20%)	Hypodiploidy (1%), t(9;22) or BCR/ABL positivity (2%), t(4;11) or MLL/AF4 positivity (2%)
Prednisone response[c]	<1000/μL blood blasts (90%)	≥1000/μL blood blasts (10%)
Early bone marrow response	<5% blasts (M1) on day 15 of induction treatment (60%)	25% blasts (M3) on day 15 of induction treatment (15%)
Remission status after induction therapy in the bone marrow (morphologically assessed)	<5% blasts (M1) after 4 to 5 weeks of induction treatment (98%)	5% blasts (M2 or M3) after 4 to 5 weeks of induction therapy (2%)
Minimal residual disease[d] in the bone marrow (molecularly assessed)	$<10^{-4}$ blasts after 5 weeks of induction treatment (40%)	10^{-3} blasts after 12 weeks of treatment (induction and consolidation) (10%)

NOTE. Prognostic factors are treatment-dependent and, therefore, the selection presented in the table cannot be entirely comprehensive; it reflects the current recommendations of the German BFM Study Group.
[a]CNS1 = puncture nontraumatic, no leukemic blasts in the cerebrospinal fluid (CSF) after cytocentrifugation; CNS3 = puncture nontraumatic, >5 leukocytes/μL CSF with identifiable blasts; TLP+ = traumatic lumbar puncture with identifiable leukemic blasts; a TLP with no identifiable blasts is not an adverse factor; the prognostic impact of CNS2 status (puncture nontraumatic, ≤5 leukocytes/μL CSF with identifiable blasts) is debated. For cytomorphological examination, CSF samples should be analyzed after cytospin preparation, a method through which cellular components within the CSF are concentrated by centrifugation.
[b]Hyperdiploidy defined as the presence of more than 50 chromosomes or a DNA index (the ratio of DNA content in leukemic G0/G1 cells to that of normal diploid lymphocytes) ≥1.16; hypodiploidy defined by <45 chromosomes; the prognostic value of MLL gene rearrangements other than MLL/AF4 and presence of the E2A/PBX1 fusion transcript are debated.
[c]After 7 days induction with daily prednisone and a single intrathecal dose of methotrexate on treatment day 1.
[d]Assessed by molecular genetic techniques or flow cytometry; markers required to have a sensitivity of at least 10–4.
ALL = acute lymphoblastic leukemia; CNS = central nervous system.
Reprinted from Stanulla M, Schrappe M. Treatment of childhood acute lymphoblastic leukemia. Semin Hematol 2009;46:52–63 (Reference 6). Copyright 2009, with permission from Elsevier.

chromosome (Ph). In this case the "t" identifies that it is a translocation, (9;22) identifies that chromosomes 9 and 22 are involved, and (q34;q11) identifies the specific sections of each chromosome that are involved. The "q" refers to the long arm of the chromosome, whereas the use of "p" would identify the short arm of the chromosome. Thus, in this example of the Philadelphia chromosome, genetic material on the long arm of chromosome 9 at segment 3, band 4 has changed places with the genetic material on the long arm of chromosome 22, segment 1, band 1 (Reference 23). Additions occur when genetic material is gained. The most common example of this is trisomy 21, in which there are three copies of chromosome 21 rather than the normal two copies. Finally, a deletion occurs when there is a loss of genetic material. Deletions can affect a section of a chromosome or an entire chromosome. For example, monosomy 7 refers to the fact that there is only one copy of chromosome 7. Table 1 reviews some of the main chromosomal abnormalities with prognostic importance. The implications of some of these abnormalities will be described in more detail later in the chapter when discussing the medical management of select subgroups of patients.

It is also important to consider the number of chromosomes in the blast cell compared with normal cells. This is referred to as the DNA index (Reference 23). A DNA index of 1.0 identifies that there is the same number of chromosomes in blast cells as in normal cells. A DNA index of more than 1, also referred to as hyperdiploidy, means that the blast cells have more chromosomes than normal cells (Reference 24). Hyperdiploidy has been associated with a favorable prognosis, partly because of the increased sensitivity to chemotherapy agents, and is generally found in patients with other favorable prognostic factors such as age and WBC count (References 24–26). Pseudodiploidy (DNA index = 1.0)

is used to describe blast cells with a normal number of chromosomes but with abnormalities such as translocations. Finally, a DNA index of less than 1, also referred to as hypodiploidy, shows that the blast cell contains fewer chromosomes than normal cells, which has been associated with a poorer prognosis (Reference 27).

Although childhood ALL is more common in boys, the male sex has been associated with a poorer prognosis than the female sex (References 10, 21). Through clinical trials and risk-adapted therapy, the impact of male sex has largely disappeared as a prognostic factor. Male patients are, however, at risk of testicular relapse as an additional site of disease. Historically, race has been identified as a factor affecting outcomes, with African American patients having a poorer outcome from therapy compared with white children (Reference 21). Results from a retrospective study showed that, although these patients were more likely to have unfavorable prognostic factors, their outcomes were similar to those of white children when treated with appropriate therapy (Reference 28).

Response to therapy is the most significant prognostic factor in childhood ALL (Reference 29). This has traditionally been measured by examining the bone marrow for the morphologic presence of leukemic blasts (greater than 5% has been correlated with a poorer response to therapy) at various times during induction and throughout therapy (References 30–33). In addition, the clearance of blasts from the peripheral blood helps predict a favorable outcome (Reference 34). Most recently, measuring minimal residual disease (MRD) has become standard practice to better assess response to therapy (Reference 35). Minimal residual disease, detected by flow cytometry or polymerase chain reaction, enables the identification of leukemic disease in the bone marrow or peripheral blood that would not have been detected morphologically. Thus, patients can now be identified as having a poor or suboptimal response when they would have otherwise been considered to have a complete response morphologically (Reference 29). The presence of MRD (MRD of 0.01% or greater) is predictive of relapse or poor response to therapy, especially in patients with high levels of MRD (MRD of 1% or greater) at the end of induction (References 29, 35, 36). The same has been true for the use of pretransplant MRD to predict the risk of relapse after transplantation (Reference 37). The ability to use MRD to risk stratify patients is being investigated in clinical trials (Reference 29).

Treatment

Therapy for childhood ALL, lasting between 2 and 3 years, has become increasingly complex as clinical trial results are incorporated into front-line treatment protocols (see Table 2 for information on the chemotherapeutic agents used in therapy) (Reference 40). Traditionally, therapy has been divided into three phases–induction, consolidation/intensification, and maintenance/continuation—with CNS-directed therapy provided throughout all phases. Current trials and therapeutic regimens have many more phases added in to intensify and add different treatment approaches, but the three general phases still exist in principle. Therapy is stratified on the basis of a patient's risk of relapse, with patients at high risk of relapse receiving more intense therapy compared with patients at low or standard risk of relapse. For this discussion on treatment approaches, we will focus on therapy for patients with precursor B-cell leukemia. The management of other patient subsets will be discussed later.

Dosing Chemotherapeutic Agents

Chemotherapy doses are most commonly calculated using a patients' body surface area, except in the infant population where doses are usually calculated based on patient weight. There are several formulas available to calculate body surface area, all of which utilize height and weight in the calculation. See the Introduction to Pediatrics chapter for an example of a body surface area equation.

Induction

The goal of induction is to induce a complete remission, which occurs successfully in around 98% of patients (Reference 40). Induction therapy usually lasts 4–6 weeks, during which time a regimen with either three or four drugs is administered (Reference 40). A three-drug induction with a glucocorticoid, asparaginase, and vincristine is used for patients with standard-risk ALL (WBC count less than 50,000; 1–9 years of age at presentation), whereas an anthracycline is added as the fourth drug in induction for high-risk patients (Reference 40). In addition to the systemic agents, intrathecal chemotherapy is given to all patients as prophylaxis against CNS relapse, regardless of CNS involvement (References 40–44). The typical 4-week induction regimen can be extended an additional 2 weeks for patients who do not achieve a complete remission at the end of induction. As discussed, response to therapy at various times during, at the end of induction, and after induction is the most important prognostic factor.

Glucocorticoids are used throughout most phases of therapy for ALL (Reference 45). The choice of glucocorticoid varies between prednisone, prednisolone, methylprednisolone, and dexamethasone, depending on the protocol. Clinical trials have shown that dexamethasone has an advantage over prednisone by improving event-free survival (EFS) and decreasing the rate of CNS relapses (References 46–48). In vitro, dexamethasone has a higher antileukemic potency than prednisone (References 45, 46, 49, 50). In addition, dexamethasone has a longer half-life and is better able to cross

Table 2. Chemotherapy Commonly Used in the Management of ALL (Reference 38)[a]

Drug Name	Class	Major Adverse Effects	Other Notes
Cyclophosphamide	Alkylating agent	Nausea, vomiting, myelosuppression, hemorrhagic cystitis, SIADH, sterility, secondary malignancy	
Cytarabine	Antimetabolite (pyrimidine analog)	Nausea, vomiting, myelosuppression, flu-like symptoms, rash, CNS changes	
Daunorubicin/ Doxorubicin	Anthracycline	Red discoloration of urine, myelosuppression, mucositis, cardiomyopathy, secondary malignancy	▪ Used mainly for high-risk patients
Etoposide	Topoisomerase inhibitor	Myelosuppression, transient hypotension, secondary malignancy	
Imatinib	Tyrosine kinase inhibitor	Fluid retention, peripheral edema, myelosuppression, peripheral neuropathies, cardiotoxicity	▪ Used for Ph+ ALL only
Mercaptopurine	Antimetabolite (purine analog)	Myelosuppression, nausea, vomiting, liver function abnormalities	▪ Administer in the evening. ▪ Take without food or milk for maximal absorption.
Methotrexate	Antimetabolite	Transaminase elevations, nausea, vomiting, mucositis, photosensitivity, osteonecrosis, nephrotoxicity	▪ Oral: administer 1 hour before or 2 hours after food or milk ▪ High-dose IV methotrexate: ensure hyperhydration, urinary alkalinization, and leucovorin administration
Nelarabine	Antimetabolite (purine analog)	Myelosuppression, nausea, peripheral neuropathies, somnolence, confusion	▪ Used in T-cell ALL only
Pegaspargase	Miscellaneous	Hypersensitivity, pancreatitis, rash, coagulation abnormalities, hyperglycemia, liver function test abnormalities, hypertriglyceridemia	▪ *Erwinia* asparaginase is an alternative product for patients with hypersensitivity to pegaspargase
Prednisone or dexamethasone	Glucocorticoid	Hyperglycemia, hypertension, Cushing syndrome, immune suppression, gastritis, infections, osteopenia, avascular necrosis	
Vincristine	Vinca alkaloid	Peripheral neuropathies, constipation, jaw pain, SIADH, foot drop, hyperbilirubinemia	▪ Fatal if administered intrathecally

[a]This table is intended to summarize adverse effects that occur commonly or are of major significance. It is not meant to be inclusive of all adverse effects or other pertinent information.
ALL = acute lymphoblastic leukemia; CNS = central nervous system; IV = intravenous; Ph+ = Philadelphia chromosome positive; SIADH = syndrome of inappropriate secretion of antidiuretic hormone.
From Reference 38.

the blood-brain barrier (References 46–48). However, the use of dexamethasone is also associated with an increased risk of infectious complications and avascular necrosis compared with prednisone (References 45, 46, 51, 52). The risk of developing avascular necrosis increases with age, with patients between 10 and 20 years of age at highest risk of developing this toxicity. Moreover, it was recently reported that the development of avascular necrosis may be related to specific genetic polymorphisms (References 52–54). Although the best way to use these glucocorticoids is not known, several approaches are being investigated in clinical trials to maximize outcome and minimize toxicity.

Asparaginase is an essential component of ALL therapy that improves outcomes when it is included in the treatment regimen (References 55, 56). Asparaginase is very effective because leukemia blast cells rely on exogenous asparagine for protein synthesis, so when

asparaginase is administered, it reduces the asparagine available for use by these cells (Reference 57). There are currently two asparaginase products that may be used during ALL therapy. Asparaginase can be derived from either *Escherichia coli* or *Erwinia chrysanthemi* (References 57, 58). *E. coli* asparaginase, also referred to as "native" asparaginase, has a half-life of about 1.4 days. Its use in therapy is limited by the inconvenience of dosing (intramuscular administration given usually three times/week, repeated for 2–3 weeks) and the incidence of hypersensitivity reactions, which have been reported to occur in as many as 60% of patients in clinical trials (References 57, 59–62). *E. coli* asparaginase has recently been removed from the U.S. market. Pegaspargase (PEGylated asparaginase), derived from *E. coli* with a half-life of about 6 days, was introduced as an option for patients with a hypersensitivity reaction to native asparaginase (References 57, 63, 64). Initial data showed that the incidence of hypersensitivity reactions with pegaspargase was lower than that with *E. coli* asparaginase; however, clinical experience has seemed to favor a more pronounced incidence of these reactions with pegaspargase than is reported in the literature. The development of these reactions may be delayed and the duration prolonged, given the half-life of the preparation (References 57, 63). However, the use of pegaspargase has replaced the use of *E. coli* asparaginase in up-front clinical trials because it is more convenient to administer, data support administering pegaspargase intravenously rather than intramuscularly, and *E. coli* asparaginase has recently been removed from the U.S. market (Reference 65). If a patient cannot receive pegaspargase, the use of *Erwinia* asparaginase can be considered, which received FDA (U.S. Food and Drug Administration) approval in late 2011. Because the source of asparaginase is different, patients are more likely to tolerate *Erwinia* asparaginase after hypersensitivity reactions to native asparaginase or pegaspargase, with overall rates of hypersensitivity reactions reported as 5% to 33% (Reference 57). *Erwinia* asparaginase has a short half-life of about 0.6 day, requiring the administration of six intramuscular doses to replace one pegaspargase dose (Reference 58). Some data show inferior outcomes from therapy when *Erwinia* is used in place of an *E. coli* asparaginase product, but other trials have not confirmed this finding (References 59, 60). The pharmacokinetics, pharmacodynamics, and dosing schemas differ between these products, so care must be taken when a different product is used to ensure the appropriate dose, route, and administration schedule (References 57, 58, 62, 63). In addition, it is important to monitor for other common toxicities that may occur with the use of asparaginase, including pancreatitis, thromboembolism, hypertriglyceridemia, hyperglycemia, and liver dysfunction (References 57, 66).

CNS Preventive Therapy

The CNS is a sanctuary site for leukemia involvement (Reference 67). The blood-brain barrier acts as an effective obstacle over which many of the systemically administered chemotherapy agents do not adequately cross; therefore, the leukemia can reside in the CNS virtually free from exposure to therapy (Reference 68). Relapse of disease in the CNS is a primary cause of treatment failure when adequate therapy is not provided to this site (References 41, 68). All patients are screened at diagnosis for CNS involvement by a lumbar puncture, with the cerebrospinal fluid (CSF) analyzed for the presence of WBCs and leukemic blasts. Because the results of the diagnostic lumbar puncture will affect the CNS-directed therapy the patient receives, the procedure should be completed by an experienced practitioner with good technique to avoid potential contamination with leukemia cells from the peripheral blood (References 69, 70). Patients are further classified as having CNS-1, CNS-2, or CNS-3 disease given the findings from the lumbar puncture. The CNS-1 disease classification identifies patients with no leukemic blasts in the CSF; CNS-2 shows the presence of blasts in the CSF with less than 5 WBCs/μL; however, patients with CNS-3 have leukemic blasts in the CSF with 5 or more WBCs/μL (Reference 8). This CNS classification is important in determining the risk of CNS relapse and the amount and intensity of CNS-directed therapy a patient will require.

All patients with childhood ALL are at risk of CNS involvement and CNS relapse, but certain features increase that risk, including patients with T-cell ALL, a high presenting WBC count, certain cytogenetic abnormalities, and CNS involvement at diagnosis (Reference 41). Intrathecal therapy, most often with methotrexate, is given to all patients concurrently with systemic chemotherapy administration as a prophylactic approach to preventing CNS relapse. In a patient who presents with CNS disease, therapy may be intensified to include additional agents (hydrocortisone and cytarabine) and/or given at a greater frequency. In addition, the choice of systemic glucocorticoid used in therapy can play a role in preventing CNS relapses because dexamethasone has fewer CNS relapses than prednisone (see previous discussion). Of note, the dosing for intrathecal therapy is based on age, not on body surface area as for most other chemotherapy agents. Age-based dosing of intrathecals allows more accurate dosing because the CSF volume changes with age, so age is a much better predictor for exposure than weight, height, or body surface area (Figure 3) (Reference 71).

In the past, cranial irradiation was effectively used as prophylaxis and treatment of ALL in the CNS. However, cranial irradiation, especially in children, is associated with many short- and long-term toxicities, including

secondary malignancies, neurocognitive dysfunction and learning disabilities, effects on growth and development, and neurotoxicity (Table 3) (Reference 41). Data now support that intrathecal therapy, used in conjunction with intensive systemic therapy, can either replace the use of cranial irradiation in most patients or allow the dose of cranial irradiation to be markedly reduced (References 5, 41–44, 72, 73). Cranial irradiation should be reserved for patients at extremely high risk of CNS relapse or in the setting of CNS relapse (Reference 41).

Post-remission Therapy

Post-remission therapy begins after the completion of induction and the successful achievement of a complete remission. Post-remission therapy generally consists of two main phases, consolidation and maintenance/continuation. As more knowledge has been gained about prognostic factors and risk stratification, additional treatment phases have been added throughout continuation/maintenance to further intensify therapy and improve outcomes. Consolidation begins after the completion of induction therapy and usually lasts between 2 and 6 months. The purpose of consolidation therapy is to introduce medications with mechanisms of action different from those used during induction to treat any remaining undetectable disease. If post-remission therapy is not administered and completed, the patient will experience a relapse of his or her leukemia, despite achieving a complete remission after induction. Typical agents used during the consolidation phase include cytarabine, methotrexate, anthracyclines, etoposide, cyclophosphamide, and intrathecal chemotherapy. The drug dosing and administration schedules are variable, depending on the protocol or treatment plan (References 3, 4, 74, 75).

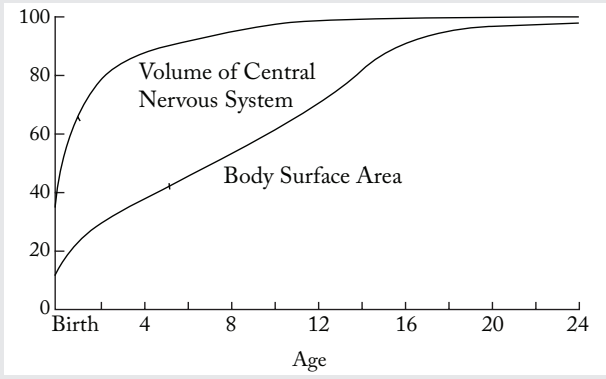


Figure 3. Relation between body surface area and central nervous system volume as a function of age.

Reprinted with permission from Bleyer W. Clinical pharmacology of intrathecal methotrexate II: an improved dosage regimen derived from age-related pharmacokinetics. Cancer Treat Rep 1977;61:1419–25 (Reference 69).

Some of the important information learned about the optimal method for administering methotrexate for ALL is noteworthy. Methotrexate has antileukemic activity and is available to be administered orally, intramuscularly, or intravenously. The use of high-dose intravenous methotrexate (at least 1 g/m^2) during consolidation improves outcomes (References 75–77). Obtaining a methotrexate serum concentration within a specific range after an infusion of high-dose methotrexate is also correlated with positive outcomes (Reference 78). A recent study showed that the duration of the methotrexate infusion can affect efficacy (Reference 79). In this study, patients were randomized to receive 1 g/m^2 of methotrexate intravenously over either 4 hours or 24 hours. The intracellular concentration of active drug, methotrexate polyglutamates, was higher in the patients receiving the 24-hour infusion, which correlated with a lower risk of relapse. In addition, another study showed that a high-dose infusion of methotrexate (5 g/m^2 per dose) had superior survival outcomes in a population of high-risk patients with ALL compared with low-dose, escalating methotrexate (Capizzi style) plus asparaginase (Reference 80). Event-free survival was improved, and the incidence of other toxicities did not increase in the patients receiving high-dose methotrexate. These are two recent examples of using information gleaned from clinical trials to support seemingly minor modifications to drug therapy to maximize outcomes with currently available agents.

Intensification of consolidation therapy has been shown in clinical trials to improve outcomes from therapy (References 81–86). This has been accomplished by adding in short phases of more intensive therapy, often called either re-induction or delayed intensification. The agents used are consistent with those used during induction and other phases of consolidation. Because of the success of these intensification regimens during consolidation and continuation, most protocols and standard treatment regimens now routinely include these additional phases of therapy.

Maintenance therapy, also referred to as continuation therapy, begins after the completion of consolidation and continues to complete a 2- to 3-year overall treatment course from the time of initial diagnosis. The purpose of this longest phase of therapy is to maintain a complete remission and prevent relapse. This therapy is less intense than what was previously prescribed and is delivered mainly in the outpatient and home settings. Maintenance therapy relies primarily on antimetabolite administration consisting of daily oral mercaptopurine and weekly low-dose oral/parenteral methotrexate (Reference 40). The doses of these agents will be modified or held, depending on the patient's response, as reflected in the WBC count, absolute neutrophil count, and platelet count (Reference 40). In addition, patients will receive

Table 3. Long-term Toxicities from Childhood ALL Therapy

Adverse Outcome	Treatment Associated with an Increased Risk	Factors Associated with Highest Risk
Neurocognitive deficits	Cranial radiation, intrathecal methotrexate, cytarabine	Females, younger age at treatment, increasing dose
Hypothyroidism	Craniospinal radiation	Increasing dose, females, age at treatment
Osteopenia/Osteoporosis	Corticosteroids, craniospinal radiation, gonadal radiation, total body irradiation	Associated hypothyroidism, hypogonadism, growth hormone deficiency
Hypogonadism	Alkylating agents, craniospinal radiation, abdominopelvic radiation, gonadal radiation	Males, treatment during peripubertal or postpubertal period in girls, higher cumulative doses of alkylators
Precocious puberty	Cranial radiation	Females, younger age at treatment, radiation dose >18 Gy
Avascular necrosis	Corticosteroids, high-dose radiation to any bone	Dexamethasone, adolescence
Growth hormone deficiency	Cranial radiation	Younger age at treatment, radiation dose >18 Gy
Obesity	Cranial radiation	Younger age at treatment (<5 years), females, higher cranial radiation dose
Secondary CNS tumor	Cranial radiation	Increasing dose, younger age at treatment
Therapy-related myelodysplasia	Topoisomerase II inhibitors	Schedule (weekly or twice weekly administration)
Skin cancer (basal cell, squamous cell, melanoma)	Radiation therapy	Orthovoltage radiation (prior to 1970)—delivery of greater dose to skin, additional excessive exposure to sun, tanning booths
Dental abnormalities	Cranial radiation	Younger age at treatment
Cataracts	Cranial radiation, steroids	Higher radiation dose, combination of steroids and radiation, single daily fraction
Chronic hepatitis C and HCV related sequelae (cirrhosis, hepatic failure, hepatocellular carcinoma)	Transfusions before 1993	Living in hyperendemic area
Cardiomyopathy/ congestive heart failure	Anthracyclines	High cumulative doses (>550 mg/m^2 in patients >18 years of age; >300 mg/m^2 for patients <18 years of age), females, younger than 5 years at treatment, African-American race

ALL = acute lymphoblastic leukemia; CNS = central nervous system; HCV = hepatitis C virus.
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intrathecal therapy at various times throughout this phase to prevent CNS relapse. Adding short pulses of more intense therapy during maintenance with vincristine and a glucocorticoid improves outcomes and is included in most treatment regimens (References 87–89).

Management of Select Patient Subgroups

T-cell ALL

T-cell ALL represents about 10% to 15% of all cases of childhood ALL and has historically been associated with worse outcomes than cases with precursor B-cell ALL (Reference 90). Reports from the late 1970s showed 3-year survival rates of around 56%, which increased to almost 80% in the early 1990s because of the intensification of therapy (References 90, 91). These patients are at an increased risk of induction failure, death during induction, early relapse, and isolated CNS relapses (Reference 91). Patients with a diagnosis of T-cell ALL are more likely to present with high-risk features including older age, an elevated WBC count greater than 50,000/μL, hepatosplenomegaly, the presence of a mediastinal mass, and CNS involvement (References 90, 92). Because of the high rates of CNS involvement at diagnosis and the increased risk of CNS

relapse, prophylactic and therapeutic cranial irradiation has routinely been administered to these patients (Reference 90). However, recent trials have shown that the dose of radiation delivered to the CNS can be minimized or even omitted without affecting overall EFS (References 90, 93–95).

Current therapy regimens for patients with T-cell ALL include the use of intensive, multiagent, systemic chemotherapy similar to that for patients with precursor B-cell ALL, in addition to CNS-directed therapy in the form of intrathecal chemotherapy and/or cranial irradiation (References 93, 95). Patients with T-cell ALL require an increased dose of systemic methotrexate (generally 5 g/m^2 rather than the 1 g/m^2 used for patients with precursor B-cell ALL) to achieve the same amount of methotrexate polyglutamates within the blast cell (Reference 5). Nelarabine, a nucleoside analog and prodrug of ara-G, is a relatively new drug that is indicated for the treatment of relapsed or refractory T-cell ALL (References 96, 97). Ara-G accumulates to a higher degree in T lymphoblasts, making this agent specifically active in the T-cell ALL population (References 96, 97). The potential role of nelarabine in combination with standard chemotherapy in the up-front management of T-cell ALL is under investigation in clinical trials (Reference 97). The most troublesome adverse effect of this drug is neurotoxicity, manifested mainly as somnolence and peripheral neuropathies (Reference 97). Treatment options for relapsed or refractory T-cell ALL include the use of a hematopoietic stem cell transplantation (HSCT).

Infant ALL

Infant ALL, defined as ALL arising in children younger than 1 year at diagnosis, accounts for about 5% of childhood ALL and is associated with a worse prognosis than ALL in older children (References 98–107). Clinical trials in this population have shown a 5-year EFS reaching only about 50%. Although this survival rate has improved through the years, it continues to be substantially lower than the survival rate in children older than 1 year at diagnosis. A potential explanation for this difference in outcome is that infant ALL is biologically different from the ALL that occurs in other pediatric age groups (Reference 108). First, there is a very high rate of chromosomal translocations with the mixed-lineage gene (*MLL*), which has been implicated as a poor prognostic indicator (Reference 109). Moreover, blast cells in infant ALL are often resistant to steroid and asparaginase therapy, which are two of the mainstays of therapy for childhood ALL, but they appear to be more sensitive to cytarabine (Reference 109).

Mutations that lead to the development of infant ALL may occur completely or partly in utero. Leukemic clones have been identified in blood obtained from neonatal heel sticks (Guthrie cards) in patients who later developed ALL, showing that some or all of these genetic events occur in utero (Reference 110). Epidemiologic studies have implicated many factors that may be associated with the development of infant ALL; however, the literature remains conflicting on most of these factors. There is a documented increased risk of developing infant ALL in patients with certain genetic syndromes (References 108, 109).

The clinical presentation of infant ALL is similar to that in other children. However, these patients are more likely to present with an elevated WBC count, hepatosplenomegaly, and CNS involvement (References 108, 109). One-half of the patients receiving a diagnosis in the first month of life will present with a condition known as leukemia cutis, which is the presence of leukemic infiltrates in the skin, resulting in a bluish purple cutaneous lesion (Reference 109).

Given the rarity of this disease in infants, it is highly recommended that all patients with infant ALL be enrolled and treated in a clinical trial available through a cooperative group. Treatment of infant ALL has been modeled after therapy for older children with the addition of high-dose cytarabine, although with poorer outcomes because of early treatment failure, namely bone marrow relapse (References 108, 109). Because of the early treatment failure, attempts have been made to intensify therapy using more aggressive chemotherapy dosing and/or an HSCT. A recent report investigating the role of HSCT in infants with *MLL* gene rearrangements did not find a survival advantage associated with HSCT compared with intensified chemotherapy (Reference 111). The use of targeted therapy in infant ALL is currently being investigated (Reference 112). FLT3, a receptor tyrosine kinase, is expressed in leukemias but is of particular interest in infant ALL because this mutation has been correlated with poor outcomes (Reference 113). Lestaurtinib, an oral FLT3 inhibitor, has potential synergy with chemotherapy and is being investigated in clinical trials (Reference 114).

Down Syndrome

Patients with Down syndrome, a genetic disorder characterized by a trisomy of chromosome 21, are at a markedly increased risk of developing acute leukemias in childhood (References 115–118). The reason behind this increased risk has not yet been identified (Reference 116). Although the clinical presentation of patients with Down syndrome is similar to that of patients without Down syndrome, there are some important differences. Patients younger than 1 year with Down syndrome do not develop ALL (Reference 116), making

the age distribution of ALL different in patients with Down syndrome. In addition, patients with Down syndrome and ALL have a lower incidence of high-risk features such as T-cell ALL, CNS involvement, hyperdiploidy, and other cytogenetic abnormalities (Reference 116). Historically, EFS rates in patients with Down syndrome were inferior to the results in patients without Down syndrome (References 116, 117). With the use of risk-adapted therapy, patients with ALL and Down syndrome can now be expected to have outcomes from therapy similar to those of patients without Down syndrome but with ALL (References 118, 119).

Patients with Down syndrome and ALL are also at an increased risk of developing toxicity from therapy, especially mucositis and infections (References 116, 120). Although the therapy for patients with Down syndrome and ALL is similar to that for patients without Down syndrome, the Down syndrome cohort is exquisitely sensitive to the effects of methotrexate (References 116, 117). The exact reason for this excess toxicity is unknown; however, potential reasons include delayed methotrexate clearance (Reference 121) and other alterations in drug handling secondary to involvement of chromosome 21 (References 116, 117). In some instances, this sensitivity to methotrexate may require dose reductions and/or more intensive rescue therapy by adding or optimizing leucovorin therapy. Other supportive care approaches to optimize care in the Down syndrome population include the use of enteral or parenteral nutrition and the use of opioids for pain management during periods of mucositis. Because these patients are at an increased risk of infections and infection-related complications, including death, prophylaxis with antibiotics, supplementation with immune globulins, close monitoring, and early initiation of empiric broad-spectrum antibiotics should be considered (References 115, 116, 118).

Philadelphia Chromosome

Caused by the translocation between chromosomes 9 and 22, the Philadelphia (Ph) chromosome is present in 3% to 5% of children with a diagnosis of ALL (References 122, 123). This genetic translocation arises when the breakpoint cluster region (BCR) gene on chromosome 22 is fused with the *ABL* gene on chromosome 9 (Reference 21). The presence of t(9;22) has been deemed a high-risk feature because it correlates with poor outcomes from traditional chemotherapy compared with patients with ALL lacking the Philadelphia (References 124–129).

Early studies that treated Ph-positive patients with intensive chemotherapy regimens, similar to the therapy described previously, showed an EFS rate ranging from 0% to 38% (References 124, 126–129). Attempts to identify high-risk features within the subset of Ph-positive patients have revealed that increased age, elevated WBC count at diagnosis, and poor response to initial therapy are associated with a poorer outcome (References 126–129). The use of imatinib, a tyrosine kinase inhibitor that competes for binding at the *BCR-ABL* site, has improved the dismal outcome of patients with Ph-positive ALL. A recent clinical trial showed the benefit of using imatinib in combination with standard chemotherapy, as evidenced by the 3-year EFS rate of the patients receiving imatinib increasing to 80% (Reference 130). This trial also raised the question of the role of HSCT in this patient population in first complete remission. Outcomes of patients who received imatinib plus chemotherapy were similar to those of patients who received stem cell transplants (Reference 130). Additional research should be completed involving more patients to truly discern the role of transplantation versus continuing traditional chemotherapy plus imatinib.

Although adding imatinib to therapy for Ph-positive patients has dramatically changed outcomes, resistance to imatinib has developed, rendering patients refractory to this therapy (Reference 131). To address this resistance issue, a second generation of tyrosine kinase inhibitors has been developed and is being investigated in pediatric Ph-positive ALL (References 131, 132). Dasatinib appears to be more potent than imatinib and has expanded activity against other tyrosine kinases (References 131, 133). Nilotinib is another second-generation tyrosine kinase inhibitor that may have benefit in pediatric patients with Ph-positive ALL (References 131, 133). It is not yet known which of these tyrosine kinase inhibitors will provide the most benefit to patients while causing the least amount of toxicity, most commonly reported as fluid retention, peripheral edema, myelosuppression, peripheral neuropathies, and potential cardiotoxicity (Reference 38).

Adolescents and Young Adults

Adolescent and young adult patients with ALL, generally defined as being between 15 and 21 years of age at diagnosis, have been identified as a population with lower survival outcomes (Reference 134). Although the exact reason for the survival differences is unknown, studies have shown that these patients have a higher incidence of T-cell ALL, have a higher presenting WBC count, are more likely to have chromosomal abnormalities associated with a poor outcome, and have a lower remission rate in induction (References 135, 136). Other potential reasons for the differences in outcome include a decreased adherence to medications, the presence of comorbidities, and an increased toxicity from therapy (References 135, 137, 138).

The young adult population, 15–21 years of age, may be managed by either a pediatric or adult oncologist, which means these patients may receive therapy designed either for pediatric ALL or adult ALL. Pediatric regimens rely on the use of long-term continuous therapy, which is heavily based on asparaginase, vincristine, and corticosteroids, whereas adult therapy uses higher doses of myelosuppressive agents such as cyclophosphamide and cytarabine, which are given intermittently for a shorter period (References 137, 139). Several studies conducted in the United States and Europe have shown superior outcomes in the young adult population when they are treated with pediatric ALL regimens rather than adult-based regimens (References 140–143). Young adult patients treated with intensive, response-based therapy had an improved outcome with chemotherapy alone and did not require stem cell transplantation (Reference 138). Thus, it is currently advised that adolescent and young adult patients be treated at a pediatric center on a pediatric clinical trial or receive pediatric-based therapy.

The adolescent and young adult population also has increased toxicity from therapy compared with younger children (References 51, 138, 144, 145). Death during induction (References 138, 144), avascular necrosis (References 51, 138), and hyperglycemia (Reference 138) occur at higher frequencies in this patient subset, potentially because of the decreased clearance rate of steroids (Reference 146). These toxicities often necessitate that therapy be modified or delayed.

Relapse

Even with major improvements in outcome over time for childhood ALL, disease relapse remains a serious problem, with survival rates in the relapsed setting reaching only 50% (Reference 147). Around 20% of patients will have a relapse of their disease at some point, with the main sites of relapse being the bone marrow, CNS, and testes (References 147, 148). It is important to consider the sites involved in the relapse and the time at which the relapse occurs because the prognosis and therapeutic approach will change on the basis of these factors (References 147, 148). An early relapse, defined as a relapse that occurs less than 36 months from initial diagnosis, has been associated with poor outcomes and often requires intensive chemotherapy to induce a second remission to proceed to stem cell transplantation (References 148–153). Late relapses, defined as those that occur 36 months or more from the initial diagnosis, will most often respond well to conventional multiagent chemotherapy, making the use of a stem cell transplantation potentially unnecessary (References 148, 152, 154). Emerging treatment regimens for relapsed ALL include the use of newer, novel agents such as bortezomib (Reference 155), epratuzumab (Reference 156), and clofarabine (References 157, 158) in combination with a standard intensive chemotherapy regimen (Reference 159).

Isolated extramedullary relapses are those that occur outside the bone marrow. An isolated extramedullary relapse is generally associated with better outcomes than an isolated marrow relapse or a relapse involving the marrow combined with other sites (References 148, 152). Around 5% to 10% of patients with a diagnosis of childhood ALL will have an isolated CNS relapse. Patients at an increased risk of CNS relapse include those with T-cell ALL, CNS involvement at diagnosis, and certain cytogenetic abnormalities, as well as those considered high risk by age and WBC count at diagnosis (Reference 152). Historically, patients with an isolated CNS relapse have been managed with intensive intrathecal and systemic chemotherapy in conjunction with CNS radiation (References 160–162). New literature supports delaying the implementation of cranial irradiation so that adequate systemic and intrathecal therapy can be delivered up front (References 160–162). Systemic, intensive, multiagent chemotherapy regimens with agents that cross the blood-brain barrier are also necessary to prevent bone marrow relapses, which were the main cause of treatment failure in the past when only CNS-based therapy was provided (References 161, 162). With this approach, about 70% of patients will be expected to achieve and maintain a complete response (References 160–162). Isolated testicular relapses occur in about 2% of patients with childhood ALL, and these relapses tend to occur late (Reference 152). Testicular relapses are managed with testicular radiation and systemic chemotherapy (Reference 152).

Supportive Care

The pediatric patient with ALL will be treated with, on average, 3 years of therapy. During this time, it is extremely important that each patient receive appropriate supportive care so that outcomes can be maximized. It is important for the pharmacist to screen for drug interactions (Reference 163), counsel the patient and his or her family on the prescribed medication regimen, and provide supportive care recommendations to the medical team.

At initial diagnosis, patients with a high tumor burden are at risk of developing TLS. In ALL, a high tumor burden is usually characterized by an increased WBC count. Tumor lysis syndrome occurs because of the lysis of WBCs, which causes the intracellular components of the cell to be released into the vasculature. This can occur spontaneously because of rapid cell turnover or upon starting therapy with chemotherapy, radiation, or even targeted therapy. Electrolyte abnormalities that can occur during TLS include hyperuricemia,

hyperkalemia, hyperphosphatemia, and hypocalcemia. The consequences of inadequate prophylaxis and treatment of TLS include acute renal failure, arrhythmias, and death. It is important to review the published guidelines and review articles for a more thorough discussion on determining a patient's risk of TLS and the literature supporting the current prevention and treatment strategies (References 164–166).

Patients with ALL may experience hematologic toxicity from therapy, resulting in the need for platelet and red blood cell transfusion. Blood counts should be followed to ensure the patient receives the appropriate blood product support. Because neutropenia occurs during therapy for ALL, the prophylactic use of granulocyte colony-stimulating factor (GCSF) has been investigated in several clinical trials for pediatric ALL. Prolonged neutropenia can put the patient at risk of infections and compromise the ability to deliver dose-intensive therapy; therefore, GCSF would be implemented in therapy to decrease these risks. Granulocyte colony-stimulating factor shortens the duration of neutropenia from chemotherapy, but this shortened duration has generally not been associated with clinically meaningful results (References 167, 168). Most clinical trials have shown that adding prophylactic GCSF does not decrease the incidence of neutropenic fever episodes, the incidence of documented culture-proven infections, or the cost associated with therapy (References 167–171). Therefore, the routine prophylactic use of GCSF is not indicated. The use of GCSF may be considered in patients with a documented, severe infection in which the timely recovery of neutrophils is critical for outcomes.

Patients with ALL are at risk of infections because of the effects of the therapy they receive. A fever that develops during periods of neutropenia should be managed as a medical emergency. It is critical that appropriate, broad-spectrum antibiotic therapy be initiated rapidly. Patients and their caregivers need to be appropriately educated about monitoring for fevers and getting the patient to the hospital as soon as possible. Clinicians should review the Infectious Diseases Society of America guidelines for neutropenic fever in the patient with cancer for additional information (Reference 172). *Pneumocystis jiroveci*, or PJP (formerly *Pneumocystis carinii* or PCP), is one of the specific infections these patients are at increased risk of developing during therapy. Patients should receive prophylaxis against PJP beginning by the end of induction and continuing for 6 months after the completion of therapy. Successful prophylaxis has been shown with sulfamethoxazole/trimethoprim (gold standard) (Reference 173), atovaquone (Reference 174), dapsone (Reference 175), and pentamidine (References 176, 177).

Malnutrition has been identified by some studies as a risk factor for poor outcomes. However, most of these clinical trials have been reported in developing countries (References 178, 179), whereas the same results have not been replicated in developed countries (Reference 180). Nutritional status plays an important role in the ability of the body to fight infections and tolerate intensive chemotherapy (Reference 181). Nutritional status should be monitored at baseline and throughout therapy, with the implementation of nutritional supplements, appetite stimulants, and/or enteral or parenteral nutrition as appropriate when a problem has been identified. To this extent, it is essential to have a dietitian as a member of the multidisciplinary health care team. On the other side of the spectrum is the emerging problem of treating overweight or obese patients (Reference 182). The obesity pandemic has brought with it a new set of challenges as it pertains to appropriate dosing of chemotherapy. It is currently unknown whether chemotherapy in the pediatric population should be dosed on body surface area calculated from actual body weight, ideal body weight, adjusted ideal body weight, or some other metric. Pharmacokinetic and pharmacodynamic studies are lacking in this area, especially for the pediatric population. To elucidate this dosing dilemma, it is important that studies be conducted and then correlated with clinical outcomes.

Monitoring of Therapy

At various times during therapy and in long-term follow-up, patients will be monitored for disease response by obtaining a bone marrow aspirate and/or biopsy and CSF from a lumbar puncture. These specimens will be analyzed using sophisticated laboratory tests to detect the presence or absence of disease. The prognostic significance of an early response to therapy, the absence of MRD, and the duration of first complete remission has been discussed earlier. At any time during or after the completion of therapy, a patient may undergo a workup to look for disease if there is a clinical suspicion that the patient has relapsed. Detecting relapses early is important to maximize the success of salvage therapy.

Late effects from childhood cancer therapy are defined as toxicities that become apparent over time after the completion of therapy, as a result of the body's inability to compensate for the increased demands that occur as a person ages (Reference 183). The development of late effects is a serious problem in childhood ALL because more than 80% of patients can be expected to become long-term survivors (Reference 184). However, because the use of cranial irradiation has been minimized as a standard therapy in ALL, the incidence of many of these late effects has significantly decreased (Reference 39). Cranial irradiation has been associated

with the development of neurocognitive deficits/learning disabilities, hypothyroidism, precocious puberty, hypogonadism, growth deficiency, obesity, secondary malignancies, and cataracts (Reference 39). Patients who receive anthracyclines as part of their therapy are at an increased risk of developing cardiac dysfunction in the form of increased left ventricular afterload and decreased contractility (References 185, 186). Most patients who receive anthracyclines for the management of ALL do not exceed lifetime cumulative doses of greater than 300 mg/m^2, above which has been associated with a markedly increased incidence of cardiotoxicity (Reference 184). The development of secondary malignancies in childhood ALL survivors, namely acute myeloid leukemia, myelodysplastic syndrome, or solid tumors, occurs at a low incidence of 1.4% to 4.2% (References 184, 187). Patients at highest risk of developing a secondary malignancy include females, patients with relapsed disease, and patients treated with radiation, anthracyclines, cyclophosphamide, and etoposide (References 184, 187–189). Infertility is not a major problem in survivors of childhood ALL (Reference 184). Patients at high risk of developing infertility include those who received testicular irradiation or who received total body irradiation or high-dose alkylating agents in the HSCT setting (References 184, 190). A good review of the risks and recommended monitoring for the late effects associated with various treatment modalities from the Children's Oncology Group Survivorship Guidelines is available at www.survivorshipguidelines.org (Reference 190). Survivors of childhood ALL require lifelong monitoring and medical care to screen for, prevent, identify early, and treat these late complications.

Future Considerations

The future of ALL therapy will involve the development of new targeted agents to maximize outcomes and minimize toxicity, particularly in certain patient subsets with suboptimal outcomes (References 112, 131). Several of these agents that are currently under investigation are bortezomib, mTOR (mammalian target of rapamycin) inhibitors, JAK (Janus kinase) inhibitors, FLT3 (FMS-like tyrosine kinase 3) inhibitors in infant ALL, NOTCH1 inhibitors in T-cell ALL, and newer tyrosine kinase inhibitors in Ph-positive ALL (References 112, 131). In addition, the use of pharmacogenomics to tailor therapy will likely become more common as research in this field advances. Pharmacogenomics or pharmacogenetics refers to the knowledge and use of genetic polymorphisms in drug-metabolizing enzymes to better understand and characterize the differences between individual responses to specific drugs and therapy (References 8, 192). The most well-established example of pharmacogenomics in childhood ALL is the knowledge of thiopurine methyltransferase (TPMT) polymorphisms to predict response to mercaptopurine therapy (References 192–195). Mercaptopurine undergoes a complex metabolic pathway to be converted from a prodrug to its active moieties, thioguanine nucleotides, and inactive nontoxic compounds (Reference 194). The metabolism of mercaptopurine occurs through activity of the enzyme TPMT. It has been identified that 90% of the population had high TPMT activity (homozygous wild type), 10% had intermediate TPMT activity (heterozygous), and 0.3% had low or no measurable enzyme activity (homozygous TPMT-deficient) (Reference 194). An increased TPMT activity level was correlated with lower levels of thioguanine nucleotide accumulation (Reference 194). Conversely, lower TPMT activity was associated with very high concentrations of thioguanine nucleotides, which led to increased bone marrow suppression and better outcomes (References 196, 197). Therefore, the *TPMT* genotype can be used to identify patients at increased risk of toxicity from mercaptopurine therapy. Rather than using the surrogate markers of absolute neutrophil count and platelet count to determine the mercaptopurine dose adjustments mentioned previously, the prospective approach of using the *TPMT* genotype to initially dose mercaptopurine is currently employed at St. Jude Children's Research Hospital (Reference 198). Current practice in most institutions is to analyze for *TPMT* polymorphisms either initially at diagnosis or when a patient does not have the expected absolute neutrophil count and platelet count response to the standard, empiric dosing of mercaptopurine. New guidelines, including dosing recommendations based on genotype, were recently published (Reference 199).

Conclusions

The role of the pharmacist on a multidisciplinary pediatric oncology team is variable, depending on the institution, but common responsibilities include verifying the accuracy of drug dosing while considering organ function and developmental concerns; confirming the point in therapy; ensuring that appropriate supportive care measures are addressed and maximized; providing education to the medical team; providing patient and caregiver counseling about drug therapy; and monitoring for expected responses and unexpected toxicities. Pharmacists are capable of contributing to the medical team, given the unique education and training they have received. In addition, pharmacists can play a vital role in contributing to clinical trial design as it pertains to drug therapy and in aiding in the conduct of these clinical trials at an institution. Pharmacists who practice in the pediatric oncology setting should become familiar

with the trials being conducted and the chemotherapeutic agents being used so that they can aid in the safe and effective delivery of therapy to these patients.

The outcomes for childhood ALL have improved drastically through the years because of a better understanding of the biology of the disease, the significance of prognostic factors, and the development of risk-adapted therapy to maximize outcomes while minimizing toxicity. Although the overall survival rates for childhood ALL are close to 90%, certain subgroups of patients still have a less favorable prognosis and outcome. Clinical trials should continue to be conducted, especially for these subgroups, to advance the knowledge and to design increasingly effective therapeutic regimens that will allow more patients to be long-term survivors. As the long-term survivor population continues to grow, it is important that these patients receive adequate long-term follow-up by experienced medical teams. These survivors need to be equipped with a thorough and complete medical history and therapeutic summary so that they can be appropriately monitored and screened for the late effects that may arise over time after the completion of therapy. With all the advances in therapy made through the years and the potential role for targeted therapy, pharmacogenomics, and response-based therapy stratification, the outlook for childhood ALL remains promising.

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CHAPTER 52

Acute Myelogenous Leukemia

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Learning Objectives

1. Understand the epidemiology and etiology of childhood acute myelogenous leukemia (AML).
2. Describe the standard approach to treating children with AML.
3. Discuss the potential role of targeted therapy in the treatment of pediatric AML.
4. Identify critical supportive care issues when treating children with AML.

Abbreviations in This Chapter

ALL	Acute lymphoblastic leukemia
AML	Acute myelogenous leukemia
APL	Acute promyelocytic leukemia
CINV	Chemotherapy-induced nausea and vomiting
CNS	Central nervous system
FLT3/ITD	FMS-like tyrosine kinase 3 internal tandem duplications
GATA1	GATA-binding protein 1 (or *GATA1* gene; globin transcription factor 1)
MLL	Mixed lineage leukemia
TMD	Transient myeloproliferative disorder

Introduction

Acute myelogenous leukemia (AML) is a term used to describe a diverse group of disorders that arise from the proliferation of abnormal myeloid, erythroid, monocytic, and megakaryocytic cell precursors (Reference 1). Although the disease-free survival of patients with AML has improved during the past 3 decades, about one-half of patients with a diagnosis of AML will succumb to this disease (References 2–15). The focus of this chapter is to review the epidemiology, etiology, prognosis, diagnosis, and treatment of childhood AML.

Epidemiology

About 12,060 children in the United States younger than 15 years receive a diagnosis of cancer each year (Reference 16). About one-third of these children are given a diagnosis of some form of leukemia, making leukemia the most common type of cancer in children (Reference 16). Of those children given a diagnosis of leukemia each year, around 18% are also given a diagnosis of AML. This reflects an incidence of about 7 in 1 million individuals younger than 19 years (Reference 17).

No known differences in incidence have been found between male and female patients. The incidence of AML appears to be highest in children of Hispanic ethnicity compared with African American or white children. Children of Hispanic descent also appear to have the highest incidence of the subtype known as acute promyelocytic leukemia (APL) (References 18–21).

Etiology

Several inherited conditions and environmental exposures have been associated with the development of de novo and secondary AML. In many cases of childhood AML, a potential cause is unknown; however, at least one known genomic alteration can be found in more than 90% of cases (Reference 22). Inherited conditions associated with the development of de novo childhood AML are identified in Box 1 (References 19, 23–37).

Down syndrome is the most common inherited condition associated with AML in children younger than 19 years in the United States. These children have a 10- to 20-fold increased risk of developing some type of leukemia compared with children without Down syndrome

Box 1. Inherited conditions associated with childhood AML (References 19, 23–37).

- Bloom syndrome
- Diamond-Blackfan anemia
- Down syndrome
- Dyskeratosis congenital
- FPD/AML
- Fanconi anemia
- Kostmann syndrome
- Li-Fraumeni syndrome
- Neurofibromatosis type 1
- Noonan syndrome
- Shwachman-Diamond syndrome

AML = acute myelogenous leukemia; FPD/AML = familial platelet disorder with a predisposition to AML.

(Reference 28). About 10% of newborn children with Down syndrome or mosaicism may develop transient myeloproliferative disorder (TMD). This incidence may be underestimated because the screening of blood counts at birth is not routine. In most patients, abnormal blasts will spontaneously disappear, and the remaining components of the blood count will normalize (Reference 38). However, almost 20% of children with TMD will develop leukemia by a median of 20 months of age; of those, most will develop the M7 subtype of AML, or acute megakaryocytic leukemia (Reference 28). One study documented that 16% of patients with TMD developed AML or myelodysplastic syndrome at a median time of 441 days (range, 118–1085 days) (Reference 38). As a result, children with Down syndrome have a 500-fold higher risk of developing acute megakaryocytic leukemia than do children without Down syndrome within the first few years of life (Reference 28). Although not fully understood, it is thought that mutation in the GATA-binding protein 1 (globin transcription factor 1, or *GATA1* gene) on the X chromosome may be an initiating factor in the development of leukemia in patients with Down syndrome. This gene is responsible in part for normal erythroid and megakaryocytic differentiation. Alterations in this gene may lead to the greater trend toward development of this leukemia in boys with Down syndrome than in girls with the same disease. Mutations in this gene have been identified exclusively in Down syndrome–associated TMD and acute megakaryocytic leukemia (References 26–28).

Environmental exposures generally associated with the development of AML include benzene, organic solvents, herbicides, pesticides, petroleum products, maternal use of marijuana during pregnancy, and previous use or exposure to chemotherapy or ionizing radiation; however, except for ionizing radiation, a definitive association of these factors with childhood AML is difficult to establish (References 19, 39–41). Maternal consumption of fresh fruits and vegetables that contribute to DNA topoisomerase II inhibition (e.g., apples, berries, canned or dried legumes, onions, soy products) may increase the risk of infant AML with rearrangements of the mixed lineage leukemia (MLL) gene (Reference 42). Chemotherapeutic agents most notably associated with the development of secondary AML include etoposide, topoisomerase II inhibitors (e.g., doxorubicin), and alkylating agents (e.g., mechlorethamine, cyclophosphamide) (References 43–47). Finally, AML may also develop after an acquired predisposing condition, such as aplastic anemia or myelodysplastic syndrome (References 48–50).

Biology and Pathophysiology

Genetic mutations or chromosomal rearrangements may result in abnormal hematopoietic precursors. Clonal transformation, replication, and proliferation of abnormal myeloid, erythroid, monocytic, or megakaryocytic precursors can result in the development of AML. Differentiation and apoptosis of these precursors is impaired, resulting in dysregulation of normal hematopoiesis. Acute myeloid leukemia develops when at least one class I and one class II mutation in a host's hematopoietic precursor cells occur. Class I mutations do not affect cellular differentiation, but they do confer a proliferative or survival advantage to hematopoietic precursor cells. Examples of clinically relevant class I alterations include FMS-like tyrosine kinase 3 internal tandem duplications (FLT3/ITD) and oncogenic *ras* mutations. Class II mutations impair the normal precursor cell differentiation and apoptosis; treatment-related examples include the *PML/RARA* fusion gene (i.e., translocation of chromosomes 15 and 17, or t(15;17)) and *MLL* gene rearrangements (e.g., t(4;22), t(11;19), t(9;11)) (References 1, 22). The prognostic significance of these alterations will be discussed later in this chapter.

Classification of AML

The FAB (French-American-British) classification system has been used historically to describe seven subtypes of AML (M1–M7) on the basis of morphologic, histochemical, immunophenotypic, and cytogenetic features of the abnormal clone (Reference 51). The M0 subtype has been used to describe undifferentiated AML. The goal of this classification system was to create uniformity in diagnosing and categorizing AML in patients. The specific criteria for each subtype will not be discussed. Subtypes of clinical importance (M0, M4, and M7) with respect to differences in therapy will be discussed throughout this chapter.

The concept of classification based on cytogenetic subtypes is still relatively new. In 2008, the World Health Organization (WHO), the European Association for Haematopathology, and the Society for Hematopathology released a revised fourth edition of their classification system of hematopoietic and lymphoid tissues. The classification of AML and related neoplasms is included in this system, the subcategories of which are described in Box 2 (Reference 52). In general, AML is defined as the presence of at least 20% myeloblasts in the peripheral blood or among all nucleated bone marrow cells. This can occur de novo or through evolution from a previously diagnosed myelodysplastic syndrome or neoplasm. However, the presence of certain translocations (e.g., t(8;21)(q22;q22), t(16;16)(p13.1;q22), or t(15;17)(q22;q12)) or the inversion of chromosome 16 (inv(16)(p13.1;q22)) is definitive for a diagnosis of AML, regardless of the blast count or percent (Reference 52). As additional information becomes available, it is possible that cytogenetics will play an even greater role in the treatment of various AML subtypes with chemotherapy and/or hematopoietic stem cell transplantation.

Box 2. WHO classification of AML and related neoplasms (Reference 52).

AML with recurrent genetic abnormalities, including the following:

- t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- t(9;11)(p22;q23); *MLLT3-MLL*
- t(6;9)(p23;q34); *DEK-NUP214*
- inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- Megakaryoblastic with t(1;22)(p13;q13); *RBM15-MKL1*
- APL with t(15;17)(q22;q12); *PML-RARA*
- Provisional entities:
  - AML with mutated *CEBPA*
  - AML with mutated *NPM1*

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

AML not otherwise specified

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

- Transient abnormal myelopoiesis
- Myeloid leukemia associated with Down syndrome

Blastic plasmacytoid dendritic cell neoplasm

AML = acute myelogenous leukemia; APL = acute promyelocytic leukemia; inv = inversion; MLL = mixed lineage leukemia; t = translocation; WHO = World Health Organization.

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Prognosis

For the past several decades, intensified chemotherapy has led to complete remission rates of 68% to 93% (References 3–15). However, relapse is relatively common, occurring in 30% to 40% of patients. The 5-year event-free and overall survival rates vary on the basis of the treatment protocol used, with these rates ranging from 31% to 54% and from 36% to 66%, respectively, as represented in Table 1 for patients without Down syndrome across several international cooperative groups (References 3–15).

The prognosis for patients with AML is affected by a variety of clinical features as well as genetic factors. In children and adolescents, age older than 10 years at diagnosis has been associated with a poorer outcome, even when controlling for potential confounding features (Reference 53). Ethnicity may also play a role in predicting prognosis. African American children have worse outcomes than white children undergoing treatment for AML. This disparity is thought to be a product of potential pharmacogenetic differences among ethnic groups, not access to care, because of the nature and delivery of cooperative group care to children with cancer (References 54, 55). Body mass index may also play a role in predicting prognosis; children who are underweight or overweight have a significantly lower chance of survival than patients who are of normal weight. This difference in survival is largely because of the increased risk of treatment-related mortality in underweight and overweight patients (Reference 56).

A retrospective evaluation of children with AML by the Children's Oncology Group revealed an 11% incidence of central nervous system (CNS) disease at presentation; children with Down syndrome–associated AML, APL, myelodysplastic syndrome, secondary AML, and isolated extramedullary AML were excluded from the analysis. Factors associated with CNS disease at presentation included younger age, hepatosplenomegaly, elevated white blood cell count (WBC), M4 morphology, abnormalities in chromosome 16, and hyperdiploidy (Reference 57). This study also found that children with CNS disease at diagnosis were at an increased risk of relapse, shortened disease-free survival, isolated CNS relapse, and concurrent bone marrow plus CNS relapse. Despite these risks, these children had similar remission rates, event-free survival, isolated bone marrow relapse, and overall survival compared with those having no CNS disease at diagnosis (Reference 57).

Pathologic disease-related features may also play a role in predicting survival. Children with AML of the M0 or M7 subtype (without Down syndrome) may have worse outcomes than those with other subtypes of AML (References 58, 59). Children with Down syndrome typically have a greater event-free survival rate

Table 1. International Cooperative Group Outcome Data for Pediatric AML (References 1, 3–15)

Study	n	CR (%)	5-yr EFS (%)	5-yr OS (%)
AIEOP92	160	89	54	60
AML-BFM93	427	83	51	58
CCG2891	750	78	34	47
DCOG-ANLL 92/94	78	82	42	42
EORTC-CLG 58,921	166	84	48	62
GATLA-AML90	179	70	31	41
LAME91	247	91	48	62
NOPHO-AML93	223	92	50	66
PINDA-92	151	68	36	36
POG8821	511	77	31	42
PPLSG98	104	80	47	50
St. Jude-AML91	62	79	44	57
UK MRC AML10	303	93	49	58
UK MRC AML12	455	92	56	66

AIEOP = Associazione Italiana Ematologia Oncologia Pediatrica; AML = acute myelogenous leukemia; BFM = Berlin-Frankfurt-Munster; CCG = Children's Cancer Group; CR = complete remission; DCOG = Dutch Childhood Oncology Group; EFS = event-free survival; EORTC-CLG = European Organization for the Research and Treatment of Cancer–Children Leukemia Group; GATLA = The Argentine Group for the Treatment of Acute Leukemia; LAME = Leucemie Aigue Myeloblastique Enfant; NOPHO = Nordic Society of Pediatric Haematology and Oncology; OS = overall survival; PINDA = National Program for Antineoplastic Drugs for Children; POG = Pediatric Oncology Group; PPLLSG = Polish Pediatric Leukemia/Lymphoma Study Group; UK MRC = United Kingdom Medical Research Council; yr = year.

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and a lower relapse rate than children without Down syndrome, especially with respect to the M7 subtype of AML. This enhanced response seen in children with Down syndrome AML may be a result of the greater sensitivity to chemotherapy, specifically cytarabine (References 60, 61).

Children with APL who receive treatment with standard chemotherapy and tretinoin (all–*trans*-retinoic acid, ATRA) may have complete remission rates greater than 95%, 5-year event-free survival greater than 70%, and overall survival of about 90% (References 62–64). Within this subgroup, an elevated WBC at diagnosis (specifically, WBC greater than 10×10^9/L) is considered a major, adverse prognostic factor with a reduced event-free survival of about 60% (References 22, 63). A small percentage of patients die during induction; about half of the deaths occur because of coagulopathy and hemorrhagic complications. Other factors associated with a poor prognosis in childhood APL include the presence of FLT3/ITD, a *bcr3 PML* breakpoint, or the microgranular variant (M3v) of the disease (References 22, 62).

Several additional cytogenetic abnormalities have been evaluated for prognostic and treatment-related purposes. In some patients, one or more of these cytogenetic abnormalities or a variety of other abnormalities may be present, making prognostic prediction and treatment decisions difficult. Some of the more notable karyotypes of blast cells that typically confer a more positive outcome include t(8;21) and inv(16). These two alterations are typically referred to as the CBF (core-binding factor) leukemias. Although they are generally grouped together in risk schema, they may differ with respect to actual outcome. Specifically speaking, patients with t(8;21) may have a lower overall survival compared with those with inv(16) because of a lower salvage rate after relapse. In patients with t(8;21), race may also play an important prognostic role (References 1, 65–67). Up to 20% of patients have *MLL* gene rearrangements at chromosome band 11q23; these patients are typically classified as having intermediate-risk disease (References 62, 68–70). Other karyotypes have been associated with a less favorable outcome, such as monosomy 5, del(5q), monosomy 7, and 3q abnormalities (Reference 62).

Other mutations that may confer prognostic significance include *c-kit*, *ras*, and FLT3/ITDs. The prognostic significance of *c-kit* and *ras* mutations in childhood AML is still unclear, and they may be of no prognostic significance (References 71–73). In adults, these have been associated with increased relapse rates and lower survival (References 74–76). FMS-like tyrosine kinase 3 internal tandem duplications in children are associated with unfavorable outcomes and are a strong predictor of relapse. Event-free survival rates for children with FLT3/ITDs may be as low as 7% to 29% (References 77, 78).

Finally, the response to initial therapy is of great prognostic significance. Children with detectable disease after the first course of induction therapy are 4.8 times more likely to relapse and 3.1 times more likely to succumb to their disease than those who achieve remission at the end of induction (Reference 79).

It is unclear how combinations of the various prognostic factors affect outcome. Much of the information available in this field is new and constantly changing. The reader is encouraged to seek additional resources for further information.

Clinical Presentation and Diagnosis

Signs and Symptoms

Leukemic infiltration of the bone marrow and extramedullary sites is responsible for most of the commonly seen signs and symptoms of AML. Children may present with anemia, neutropenia, and thrombocytopenia as the normal hematopoietic cells within the bone marrow are replaced by the abnormal clone. As a result, pancytopenia, fever, fatigue, pallor, bleeding, bone pain, and infectious complications may occur. In some cases, patients may present with hyperleukocytosis at diagnosis instead of neutropenia or leukopenia. Lymphadenopathy, hepatosplenomegaly, chloromas, leukemia cutis, gum swelling and/or bleeding, and orbital swelling can result from extramedullary involvement of the leukemic clone (Reference 1).

Patients with Down syndrome may initially present with TMD weeks to months before AML develops. Transient myeloproliferative disorder, which has also been referred to as transient abnormal myelopoiesis or transient leukemia, may present on a spectrum from an incidental finding of blasts in the blood in a well-appearing child to a variety of severe complications including effusions, hydrops fetalis, and multiorgan system failure (Reference 28).

Patients with APL may present with signs and symptoms similar to those of children with AML. In addition, they often present with a specific coagulopathy that is a combination of fibrinolysis and disseminated intravascular coagulation (Reference 80). Emergency management of the presenting coagulopathy and underlying disease state is critical.

Diagnostic Criteria

A diagnosis of AML is based on a combination of tests that are typically performed on a sample obtained during a bone marrow aspirate and biopsy. Diagnostic tests include morphologic evaluation, cytogenetic and cytochemical analysis, fluorescence in situ hybridization, immunophenotyping by flow cytometry, and molecular testing (Reference 1). Lumbar puncture should be performed to determine the presence and extent of any abnormal myeloblasts in the CNS.

Treatment

Chemotherapy Overview

Improvement in the survival of children with AML is partly because of refinement in the use of conventional chemotherapeutic agents. Each of the international cooperative groups previously mentioned in Table 1 stratified therapy on the basis of various risk classifications and features. Therapy for each group involved intensive induction chemotherapy, followed by aggressive post-remission chemotherapy. Similar agents were used throughout each phase of therapy, including cytarabine, etoposide, and an anthracycline (i.e., daunorubicin, idarubicin, or mitoxantrone). Doses of each of the agents varied widely across groups. Among the 14 cooperative groups, cumulative doses of cytarabine ranged from 3.8 to 55.7 grams/m^2, with about one-third of the groups giving cumulative cytarabine doses exceeding 30 grams/m^2. Cumulative doses of etoposide varied as well, from 400 to 2250 mg/m^2. Cumulative doses of anthracyclines varied from 180 to 610 mg/m^2 (expressed in daunorubicin dosing equivalents); almost all groups used doses exceeding 300 mg/m^2, with some using cumulative doses as high as 610 mg/m^2. In some patients, myeloablative hematopoietic stem cell transplantation was employed as a component of post-remission therapy (References 1–15).

The optimal anthracycline and its corresponding dose recommended for use in pediatric AML have yet to be determined. The use of idarubicin is at times recommended as the anthracycline of choice because it has shown faster cellular uptake, increased retention, and reduced susceptibility to resistance in preclinical and in vitro studies (References 81, 82). In a clinical trial using cytarabine and etoposide, the addition of idarubicin showed statistically greater blast clearance at induction day 15 compared with daunorubicin, yet it did not result in a greater event-free or overall survival at 5 years. In this study, patients who received idarubicin also had more bone marrow toxicity and exhibited a longer time to bone marrow recovery than patients who received daunorubicin (Reference 83). A later trial indicated that daunorubicin and idarubicin were similarly effective when a daunorubicin dose of 50 mg/m^2 was compared with an idarubicin dose of 10 or 12 mg/m^2. This trial also showed that at these comparable doses, the use of idarubicin resulted in more renal, gastrointestinal, and pulmonary toxicities (Reference 84). Daunorubicin and mitoxantrone have shown similar efficacy, yet slightly different toxicity profiles, with mitoxantrone being more myelosuppressive (Reference 15). Pediatric patients may be at a greater risk

of developing cardiotoxicity from anthracyclines; therefore, some investigators have sought to determine whether the cumulative dose of anthracycline used can be reduced (Reference 1). To date, this dose has yet to be defined.

Chemotherapy for the treatment of AML is typically divided into two phases: induction and post-remission, or consolidation, therapy. Maintenance therapy, although typically used in acute lymphoblastic leukemia (ALL), is not used routinely but will be discussed briefly. A general schematic of the treatment of AML is provided in Table 2. Selected common and distinguishing toxicities of chemotherapy used in the treatment of AML are provided in Table 3.

Induction Therapy

The goal of the induction phase of therapy is to eliminate the disease to the point of remission. Although the cumulative dose of cytarabine given for the duration of therapy appears to be important, the specific dose and frequency of cytarabine during induction do not appear to significantly affect outcomes. Various doses of cytarabine have resulted in similar complete response rates (References 1–15, 87). On the contrary, the dose of the anthracycline used during induction may be of critical importance (References 1–15, 83). In previously untreated adults with AML, a higher dose of daunorubicin (90 mg/m^2) given as three daily doses during the induction phase of therapy provided a statistically higher complete remission rate and overall survival compared with a lower dose of 45 mg/m^2 (Reference 88). The optimal dose of anthracycline for children with AML is unclear; it is possible that doses of 375–550 mg/m^2 are necessary because protocols using anthracycline doses (in daunorubicin equivalents) of less than 375 mg/m^2 report lower event-free survival (Reference 1). These higher doses are assumed to increase the risk of developing cardiotoxicity, but this has not been characterized (Reference 1).

Table 2. Overview of the Treatment of AML

Patient Subgroup	Phase of Therapy	Agents Employed[a]
Non–Down syndrome	Induction (two cycles)	Standard- or high-dose cytarabine + etoposide + anthracycline
	Post-remission/ Consolidation (two or three cycles[b])	High-dose cytarabine + one of the following (per cycle): • Etoposide • Mitoxantrone OR idarubicin • L-Asparaginase
Down syndrome	Induction (two to four cycles)	Standard-dose cytarabine + daunorubicin (or mitoxantrone) + thioguanine High-dose cytarabine + L-asparaginase[c]
	Consolidation/ Intensification (two or three cycles[a])	Standard-dose cytarabine + one of the following (per cycle): • Etoposide • Mitoxantrone • L-Asparaginase
Acute promyelocytic leukemia	Induction	ATRA + idarubicin
	Consolidation	ATRA + one of the following (per cycle): • High-dose cytarabine + mitoxantrone • Mitoxantrone + etoposide • High-dose cytarabine + idarubicin ± thioguanine • Arsenic trioxide (investigational)
	Maintenance	ATRA + mercaptopurine + methotrexate

[a]Agents employed will vary on the basis of institutional practice and clinical protocol or trial. These agents are representative of some of the types of combinations used in the respective disease state.

[b]Patients at a high risk of relapse with a matched donor may proceed to hematopoietic stem cell transplantation on the basis of institutional practice or protocol-directed therapy.

[c]May be used in some centers for one cycle.

AML = acute myelogenous leukemia; ATRA = all–*trans*-retinoic acid.

References 1-15, 60, 62-64, 85, 91.

Post-remission/Consolidation Therapy

Post-remission, or consolidation, therapy is given with the intent of eliminating any residual disease. For many patients, chemotherapy given in the post-remission phase will include two or three additional courses of high-dose cytarabine with other active agents, such as etoposide, mitoxantrone, idarubicin, or L-asparaginase. In this setting, the use of high-dose cytarabine appears to be of greater benefit than standard or low-dose cytarabine in some patients with AML. Specifically, adult patients with t(8;21) who were given three or more courses of chemotherapy with high-dose cytarabine in the post-remission period had improved failure-free and overall survival compared with those who received only one course of post-remission chemotherapy that included high-dose cytarabine (Reference 89). Similarly, adult patients with inv(16) and t(16;16) had a significantly lower cumulative incidence of relapse and a trend toward a reduction in relapse-free survival with three or four courses of high-dose cytarabine-containing chemotherapy compared with one course in the postinduction period (Reference 90). A clinical trial involving both children and adults with previously untreated AML found no difference in relapse rate, relapse-free survival, death in complete remission, or overall survival when patients were administered four versus five courses of chemotherapy (i.e., two vs. three courses of chemotherapy in the post-remission or consolidation phase) (Reference 91).

Considerable controversy still exists regarding the appropriate type and use of stem cell transplantation in children with AML in first remission. Complicating matters, international cooperative groups use various risk criteria

Table 3. Common and Unique Toxicities of Chemotherapy for AML[a]

Agent	Toxicities
Arsenic trioxide	Tachycardia, prolongation of the QT interval, edema, hypotension, insomnia, anxiety, dizziness, depression, dermatitis, bruising, hypokalemia, hyperglycemia, hypomagnesemia, nausea, vomiting, sore throat, constipation, anorexia, leukocytosis, APL syndrome, anemia, transaminitis, pain, rigors, paresthesias, cough, dyspnea, hypoxia, pleural effusion, epistaxis, sinusitis, diarrhea, fatigue, fever, headache, pruritus
L-Asparaginase	Anaphylaxis, fever, chills, nausea, vomiting, abdominal cramping, seizures, coma, azotemia, coagulopathy, hypofibrinogenemia, decreased clotting factors, decreased antithrombin III, hepatotoxicity, pancreatitis, hyperglycemia
ATRA	Arrhythmias, chest discomfort, dyspnea, respiratory insufficiency, pleural effusion, edema, weight gain, shivering, dizziness, pain, pruritus, nausea, vomiting, diarrhea, earache/ear fullness, fever, malaise, flushing, rash, headache, hypercholesterolemia, hypertriglyceridemia, leukocytosis, mucositis, hemorrhage, disseminated intravascular coagulation, retinoic acid syndrome, skin/mucous membrane dryness, increased liver function tests, infection
Cytarabine	Conjunctivitis (w/high-dose use steroid eye drops), rash, alopecia, anorexia, diarrhea, fever, malaise, nausea, vomiting, mucositis, myelosuppression, neurotoxicity (cerebellar toxicity, confusion, seizures, tremor), hepatotoxicity, thrombophlebitis
Daunorubicin and idarubicin	Cardiomyopathy (may be delayed), transient ECG changes, mucositis, myelosuppression, radiosensitizer, vesicant if extravasated, nausea, vomiting, red discoloration of urine
Etoposide	Anaphylaxis, hypotension, irritant if extravasated, mucositis (with higher doses), myelosuppression, alopecia, nausea, vomiting
Mercaptopurine (6-MP) and thioguanine (6-TG)	Hepatotoxicity, myelosuppression, pancreatitis (6-MP), sinusoidal obstruction syndrome (6-TG), drug fever, alopecia, hyperpigmentation, rash, diarrhea, hyperuricemia, anorexia
Methotrexate	Nausea, vomiting, diarrhea, anorexia, mucositis, myelosuppression, neurotoxicity, rash or reddening of skin, renal failure, nephropathy, transient transaminitis
Mitoxantrone	Cardiomyopathy (may be delayed), arrhythmia, edema, fever, pain, fatigue, alopecia, nausea, vomiting, diarrhea, anorexia, mucositis, amenorrhea, myelosuppression, hyperglycemia, transaminitis, increased BUN, bluish discoloration of sclera, fingernails, and urine

[a]This list is not meant to be inclusive, but rather, representative of the more common or distinguishing toxicities of each agent.
AML = acute myelogenous leukemia; APL = acute promyelocytic leukemia; ATRA = all–*trans*-retinoic acid; BUN = blood urea nitrogen; ECG = electrocardiogram.
Reference 86.

and stratification to determine which patients should receive a transplant in first remission as part of post-remission or consolidation therapy. It is generally accepted that children with APL, Down syndrome, inv(16), or t(8;21) have considerably better outcomes than other patients with AML and that stem cell transplants in first remission could result in excess toxicity without a survival advantage (Reference 1). Retrospective data suggest that an allogeneic stem cell transplantation from a matched sibling donor provides a survival benefit over additional chemotherapy for patients with intermediate-risk AML. On the basis of these data, it is assumed that the same would be true for patients with high-risk disease (e.g., patients with deletions of 5q, monosomy 5 or 7, or more than 15% blasts remaining after the first course of chemotherapy) (References 92–94). It is possible that patients who receive a matched sibling transplant have a reduced risk of relapse without a corresponding improvement in overall survival (Reference 15). The risk of secondary malignancy and the potentially severe toxicities incurred because of stem cell transplantation should be balanced with a significant survival advantage; to date, this transplant advantage is unclear in any subgroups of children with AML (References 92–94).

Maintenance Therapy

Although critically important in pediatric ALL, maintenance therapy does not play a role in the treatment of most types of pediatric AML. Overall survival for patients who did not receive maintenance therapy was significantly higher than for patients who received maintenance therapy for up to 18 months (Reference 95). The reduction in overall survival may have been caused by the development of drug resistance and subsequent treatment failure (Reference 95). Acute promyelocytic leukemia appears to be the only type of AML for which maintenance therapy is important in maintaining remission. Patients with APL who receive tretinoin together with chemotherapy during induction and maintenance have improved response and survival (Reference 62).

CNS Therapy

Unlike its role in the treatment of pediatric ALL, the role of CNS-directed therapy in pediatric AML is unclear. The use of systemic high-dose cytarabine and idarubicin is thought to contribute to the treatment or prophylaxis of CNS disease in pediatric AML (Reference 96). Up-front cranial irradiation is not widely used by various international cooperative groups and is not used for the treatment of pediatric AML in the United States (References 1, 97). It is used in some patients who do not clear leukemic blasts from the CNS after systemic and intrathecal chemotherapy (References 5, 12, 14). The use of cytarabine alone or triple-agent (cytarabine, hydrocortisone, and methotrexate) intrathecal chemotherapy may be used for CNS prophylaxis in children with AML or treatment of those with abnormal myeloid precursors in the CNS at diagnosis (Reference 1).

Special Exceptions

Children with Down Syndrome

Children with Down syndrome are uniquely sensitive to chemotherapeutic agents active in the treatment of AML. Myeloblasts in children with Down syndrome and AML exhibit enhanced activation and reduced metabolism of cytarabine. This is likely the result of the mutant *GATA1* gene seen in these patients, which results in the increased expression of deoxycytidine kinase and cystathionine β-synthase together with decreased expression of cytidine deaminase (References 60, 98, 99). This enhanced sensitivity is likely related to the greater treatment-related toxicity and mortality seen in children with Down syndrome. A reduction in the dosing of conventional chemotherapy may result in improved survival because of a reduction in treatment-related mortality (Reference 85).

Acute Promyelocytic Leukemia

Historically, APL has been treated with standard chemotherapy (cytarabine plus anthracyclines) in induction and consolidation/post-remission therapy, like other types of AML. Some studies have used daunorubicin as the anthracyclines of choice, whereas others have used idarubicin or mitoxantrone. Tretinoin was recently added to standard chemotherapy with success (References 62–64). As previously mentioned, the t(15;17) translocation fuses the *PML* gene on chromosome 15 to the retinoic acid receptor (*RAR*) gene on chromosome 17 (Reference 80). Tretinoin is recognized as the first molecularly targeted pharmacologic agent in the treatment of acute leukemias because of its ability to destabilize the *PML-RAR* complex, permitting the expression of genes that allow differentiation of the abnormal clone (Reference 22).

Patients with APL treated with tretinoin may experience a unique collection of adverse events in the first few days to weeks after beginning therapy. This condition, retinoic acid syndrome, may occur in 6% to 27% of patients and be more pronounced in children than in adults. Retinoic acid syndrome has been associated with increasing WBCs, fever, weight gain, dyspnea, pleural effusion, pulmonary infiltrates, and pseudotumor cerebri (Reference 80). Pseudotumor cerebri, which is characterized by increased intracranial pressure, visual abnormalities, and papilledema, may occur without other complications of retinoic acid syndrome and may be more common in children (References 62, 63, 100). The management of pseudotumor cerebri may require the dose reduction or discontinuation

of tretinoin and the administration of corticosteroids, analgesics, and mannitol (Reference 100). In some patients, renal failure, hypotension, and pericardial effusion may also occur. The mechanism of this syndrome is not well understood, but it is speculated to involve the release of cytokines from the APL cells undergoing differentiation (Reference 80). Medical management of the patient in the critical care unit is often required.

Improved outcomes through the years have been associated with intensive treatment with anthracyclines, including cumulative doses as high as 400–750 mg/m^2 (Reference 101). These higher doses of anthracyclines increase the risk of late cardiotoxicity in children and have led investigators to examine ways to reduce total anthracycline exposure (Reference 22). Of particular interest is the utility of arsenic trioxide in the management of relapsed/refractory and children with newly diagnosed APL (References 102–107). A recent cooperative group clinical trial evaluated the effect of arsenic in the consolidation phase in lieu of an anthracycline-containing course with the aim of reducing anthracycline exposure while maintaining a high survival rate (Reference 108). Preliminary data from this study of children with APL suggest that the substitution of arsenic in the consolidation phase has similar efficacy with respect to event-free and overall survival; in adult patients, the addition of arsenic significantly improved event-free and overall survival (Reference 109). This trial also used high-dose cytarabine on the basis of data showing a higher event-free and overall survival together with a reduced relapse rate in patients receiving cytarabine plus daunorubicin (Reference 108). Tretinoin is used in the maintenance phase along with chemotherapy (References 22, 62).

Therapy for Relapsed Disease

Survival after relapse is low. Only 21% to 33% of patients who receive chemotherapy for the treatment of relapse survive (References 110–115). Agents that have been used in the treatment of relapsed disease include fludarabine, clofarabine, and cladribine as well as the agents used during the initial treatment of the disease (e.g., cytarabine, etoposide, daunorubicin, idarubicin, and mitoxantrone). Various combinations have been studied, including fludarabine plus cytarabine, fludarabine plus cytarabine and idarubicin, clofarabine monotherapy, clofarabine plus cytarabine, and clofarabine plus cytarabine and etoposide (References 116–120).

The length of first remission is an important predictor of long-term survival (References 111–113). An evaluation of prognostic factors for survival in children with relapsed AML found that the only independent variable associated with outcome was the time to relapse. Specifically, children who relapsed after a disease-free period of at least 18 months (1.5 years) had a statistically higher long-term survival, regardless of whether they received chemotherapy alone or chemotherapy plus stem cell transplantation (Reference 111). Children with a late relapse had a 5-year survival estimate of 40% (standard error [SE] 10%), whereas those relapsing earlier (i.e., within 1.5 years from the end of previous therapy) had a 5-year survival estimate of 10% (SE 5%) (Reference 111). Patients who receive a stem cell transplant after an early relapse can be expected to have a 56% chance of survival at 5 years compared with 65% at 5 years for late relapse (Reference 115).

Future Approaches and Targeted Agents

Future approaches to improving outcomes in childhood AML may include earlier incorporation of newer agents such as clofarabine into front-line treatment protocols, enhanced supportive care techniques to support intensive chemotherapy, and further refinement of the role and timing of stem cell transplantation. Additional approaches should focus on a greater understanding of the biologic features of the disease and the development of targeted therapies that improve survival without increasing treatment-related mortality. Agents under consideration include proteasome inhibitors (e.g., bortezomib) and tyrosine kinase inhibitors (e.g., sorafenib)(Reference 122).

The tyrosine kinase inhibitors targeting FLT3 are of particular interest in the treatment of childhood AML because about one-fourth of younger adults with AML possess internal tandem duplications of the *FLT3* gene (Reference 121). Sorafenib is a tyrosine kinase inhibitor which has expressed activity in treating patients with FLT3/ITDs. Sorafenib, which among other targets is also known to inhibit the Raf-1 kinase and subsequently the Raf/MEK/ERK pathway, is approved by the U.S. Food and Drug Administration for the treatment of hepatocellular carcinoma and renal cell carcinoma (Reference 121). A phase I/II clinical trial of sorafenib, idarubicin, and cytarabine in adults with AML showed a clear response to sorafenib; however, the risk of relapse was not eliminated, even in patients with FLT3/ITDs (Reference 121). A phase III clinical trial by the Children's Oncology Group is evaluating the efficacy of sorafenib or bortezomib in addition to conventional chemotherapy for children with newly diagnosed, previously untreated AML (Reference 122).

Supportive Care

Supportive care is critical to minimize toxicities and treatment delays. As with patients having other hematologic malignancies, patients with newly diagnosed AML must receive close monitoring and treatment for tumor lysis syndrome, infection, and various hematologic complications. Clinical tumor lysis syndrome, defined as laboratory findings of tumor lysis syndrome plus at

least one clinical complication (i.e., cardiac arrhythmias/sudden death, renal insufficiency, seizures), has been reported to occur in 3.4% to 5% of children with AML; this is slightly less than the incidence of tumor lysis syndrome in children with ALL (5.2%) and non-Hodgkin lymphoma (6.1%) (Reference 123). Children with newly diagnosed AML and a total WBC greater than 50,000 have been characterized as being at high risk of developing tumor lysis syndrome (Reference 123). Tumor lysis syndrome can be prevented or managed through the aggressive use of oral or intravenous hydration, electrolyte monitoring and prompt correction. Either rasburicase or allopurinol is used in the treatment of tumor lysis syndrome on the basis of an institution's preference. Given an evidence-based review of tumor lysis syndrome, rasburicase may be a better option in AML, as clinically appropriate (Reference 123). Hematologic parameters may require correction through packed red blood cell or platelet transfusions and, in some cases, exchange transfusions or leukapheresis.

Patients with AML are at an increased risk of a variety of infectious complications because of prolonged periods of neutropenia. Patients with AML who develop febrile neutropenia should receive treatment with broad-spectrum antibiotics in a closely monitored inpatient setting. Empiric antibiotics administered to the febrile, neutropenic patient with AML should at minimum include appropriate coverage for gram-negative enteric bacteria and viridans streptococci. Of note, patients who have recently received high-dose cytarabine are at increased risk of developing sepsis from viridans streptococci (Reference 124). A retrospective analysis of the use of prophylactic antibiotics revealed that the use of cefepime and vancomycin can significantly reduce the risk of general bacterial sepsis as well as streptococcal sepsis (Reference 125).

Because of the high risk of invasive fungal infection in patients with AML, many treatment protocols now recommend or require the use of an antifungal agent as prophylaxis. For patients who develop febrile neutropenia, broad-spectrum antifungal agents (e.g., amphotericin products, echinocandins, or voriconazole) should be considered. For severe cases of sepsis or prolonged neutropenia, the addition of granulocyte colony-stimulating factors should be considered (Reference 1). In some cases, granulocyte transfusions may also be considered.

One of the greatest concerns for patients with cancer is the development of chemotherapy-induced nausea and vomiting (CINV). The introduction of 5-HT3 (serotonin-5 receptor) antagonists (e.g., dolasetron, granisetron, ondansetron) has improved the prevention and treatment of CINV (Reference 126). These agents are now routinely used as front-line agents to manage this complication in children with cancer. Adjunctive agents such as promethazine, prochlorperazine, metoclopramide, diphenhydramine, and lorazepam are also used. Although dexamethasone is an effective antiemetic, many centers avoid its use in patients with hematologic malignancies for various reasons; in patients with AML, the routine addition of dexamethasone or other corticosteroids holds the potential of increasing the already high risk of developing invasive fungal disease. In adult patients with CINV, the neurokinin 1 receptor antagonist, aprepitant, has significantly improved CINV management (Reference 127). In children and adolescents, it has shown less promise (References 128–130). Moreover, the concern for potential drug-drug interactions cannot be ignored because of the effect of aprepitant as an inhibitor of the cytochrome P450 3A4 isoenzyme (Reference 131).

Late Effects

All children who receive chemotherapy for the treatment of a malignancy should receive long-term monitoring. Long-term follow-up should include plans to monitor for treatment-related toxicities as well as disease recurrence. Children with AML who are in remission after treatment with chemotherapy are at an increased risk of developing several late effects, depending on the agents included in the treatment regimen. For any child who receives an anthracycline, long-term follow-up must include monitoring for cardiac toxicities, specifically left ventricular hypertrophy. Most children will require a vaccination "catch-up" schedule based on the time of diagnosis and the number of vaccines missed during the treatment period. Children who receive a stem cell transplant will require additional interventions, such as revaccination with any vaccines received before transplantation. The reader is encouraged to refer to the Children's Oncology Group *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers* for additional information on the appropriate timing and selection of evaluation criteria and markers for survivors of childhood cancer (Reference 132).

Conclusions

Childhood AML continues to be a difficult malignancy to treat. Merely half of patients with newly diagnosed AML can be expected to have a long-term survival. Significant progress in recent years has occurred in the treatment of APL, a subtype of AML. Survival in these patients exceeds that of other subtypes because of the development of targeted therapy for the specific genetic alteration seen in the disease. Although genetic associations have been seen in other patients with AML, a successful targeted therapy has yet to be discovered. Further refinement and understanding of the genetic alterations responsible for disease development and progression are necessary for targeted drug development. Future

clinical trials will focus on the treatment of childhood AML with various targeted therapies and other investigational agents, techniques to minimize the late effects of chemotherapy, and the role and timing of hematopoietic stem cell transplantation.

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CHAPTER 53

Pain Management

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Learning Objectives

1. Describe the impact of neurobiologic changes on the development of pain in pediatric patients.
2. Recognize two differences in pain management in children compared with adults.
3. Differentiate between five different pain scales used for pain assessment in children.
4. Identify the pharmacokinetic and pharmacodynamic effects of non-opioids and opioids in children.
5. Select an appropriate agent for acute and chronic pain on the basis of severity and location of pain.
6. Compare and contrast agents used for procedural sedation in neonates and children.

Abbreviations in This Chapter

AAP	American Academy of Pediatrics
ADME	Absorption, distribution, metabolism, excretion
FLACC	Face Legs Activity Cry Consolability Scale
LET	Lidocaine, epinephrine, and tetracaine
NCA	Nurse-controlled analgesia
NCCPC-PV	Non-communicating Child's Pain Checklist-Postoperative Version
NRS	Numerical rating scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCA	Patient-controlled analgesia

Introduction

Pain management in children is a unique challenge for pharmacists and other health care professionals. Children admitted to the hospital or seen at an emergency department or outpatient clinic may experience several different etiologies of pain including acute pain (e.g., diagnostic and therapeutic procedures, oral/nasal/tracheal suctioning), established pain (e.g., thermal/chemical burns, postsurgical pain), prolonged pain (e.g., meningitis, necrotizing enterocolitis), and chronic pain (e.g., sickle cell disease) (Reference 1). Pain pharmacotherapy is associated with many challenges for clinicians, not limited to assessment and treatment. The heterogeneity of the pediatric population makes it difficult for a one-size-fits-all approach. Inadequate pharmacotherapy can be associated with adverse physiologic changes, especially in the neonatal population. In children, analgesics are among the highest class for medication errors, and there are several medication safety concerns that pharmacists should consider when developing pain care plans.

Historically, there have been many misconceptions regarding the definition, recognition, and management of pain in infants and children compared with that of adults. In the 1970s, the International Association for the Study of Pain Subcommittee on Taxonomy defined pain as "an unpleasant sensory emotional experience associated with actual or potential tissue damage" (Reference 2). Inherent in this definition was the idea that pain is a learned response. Another common misconception was that neonates could not feel pain, and even if they did, they would not remember the experience (Reference 3).

Because of these misconceptions, evidence suggests that children have suboptimal pain treatment compared with adults. In the 1980s a retrospective study comparing analgesic usage patterns in 90 children and 90 adults matched for sex and diagnosis was conducted (Reference 4). The investigators found that children received fewer opioid doses compared with adults but concluded that it is was challenging to know whether these findings were related to discrepancies in pain assessment or other factors. More recent studies have identified that untreated pain is associated with significant behavioral and biochemical consequences (References 5–7). Clinically, these consequences may result in delayed healing, complicated recovery time, and significant stress not only for the patient but also for the patient's caregivers. Because of the emerging research in this population, researchers have proposed a new definition of pain that states "pain perception is an inherent quality of life that appears early in development to serve as a signaling system for tissue damage" (Reference 8). The system is composed of both physiological and behavioral indicators that can adequately depict pain and others can interpret (Reference 8).

Physiology of Pain Transmission

Studies during the past 20 years have explored pain perception among young infants and adults. Research has confirmed that although pain perception is similar among adults and neonates, the differences between the two have been primarily attributed to neurophysiologic and cognitive immaturity (Reference 9). To understand these differences in more detail, it is important to review the physiology of pain stimulation, transmission, perception, and modulation. The first step in the development of pain involves the sensation of painful or noxious stimuli leading to the excitation of nerve endings called nociceptors in the periphery. Several different mediators including bradykinin, prostaglandin, histamine, substance P, and serotonin have been associated with the sensitization and activation of nerve transmission in concert with the noxious stimuli. These mediators may be a source for targeted intervention (Reference 10). Activation of nociceptors results in transmission of nerve impulses along the ascending pain pathway from the periphery along A-delta and C-afferent nerve fibers to the dorsal horn of the spinal cord. The A-delta nerve fibers are myelinated, large-diameter fibers that allow sharp, localized pain response. The C-afferent fibers are unmyelinated fibers, representing the most common path for nociception in both neonates and adults, and result in dull, aching, poorly localized pain. The nerve impulse is then transmitted along various spinal tracts, including the spinothalamic tract to the thalamus. Once the signal reaches the thalamus, the patient is able to become consciously aware of the source of pain and is able to localize the origin of the pain (Reference 11). Modulation of the pain response occurs through the descending pain pathway when a series of supraspinal structures, including the locus coeruleus and rostral ventromedial medulla, directly or indirectly alter the pain transmission from the brainstem to the spinal dorsal horn (Reference 10). The net result of modulation is that nociception of the painful stimuli is either inhibited, leading to pain inhibition, or facilitated, leading to exacerbation of the pain response.

Differences in Pain Management in Children vs. Adults

Even though the pathways for pain perception through modulation are essentially the same in all populations, several neurophysiologic factors in neonates make pain management unique in the neonatal population. The elements of the peripheral and central nervous system necessary for pain transmission and perception develop in the fetus at the end of the first trimester (Reference 12). Evidence suggests the fetus has the ability to perceive pain even before birth; however, the structures necessary for pain modulation through the descending pain pathway are not complete until 30–32 weeks' gestation (Reference 1). The final stage of neural development is complete at 37 weeks' gestation with the integration of a myelin sheath around the spinothalamic tract (Reference 12). In addition to the environmental and disease state factors that may be a source of pain in neonates, the developmental maturity (i.e., gestational age and postnatal age) of the neonate can contribute to differences in pain perception and modulation between neonates and adults. Because premature neonates younger than 32 weeks' gestational age do not have a fully developed descending pain pathway, they have been shown to experience a lower pain threshold and even a hypersensitivity that develops as a result of repeated painful procedures (References 1, 13). In addition, infants have less-precise pain transmission than older infants and children. The touch and pain transmission pathways are close to each other on the spinothalamic tract (Reference 12). Because of the infant's decreased accuracy in pain perception, he or she may lose the ability to differentiate a painful response from a non-painful response. Research has shown that neonates experience pain and that the early pain responses they experience are associated with long-term changes in pain perception (Reference 12).

In addition to the neurophysiologic factors, other differences in pain management between adults and children must be recognized. There are cognitive and developmental differences in young children that make it difficult to assess and treat pain. Clinicians should also note specific factors in children that may affect the dose of an analgesic medication or even the selection of particular analgesics. Small children may have high oxygen consumption and smaller lung volumes, so they may be more prone to periods of apnea when they are administered opioids or sedative medications to relieve pain and anxiety (Reference 14). In such cases, a dosage adjustment may be required to avoid adverse events. The absorption, metabolism, and excretion of selected pain medications may also be altered in pediatric patients requiring a dosing adjustment compared with adults.

An abundant amount of data suggests the significance of pain in children. As a result, several different organizations have emphasized the need for pain assessment in children (References 15, 16). In 2001, the Joint Commission implemented pain management standards that mandated health care facilities to execute uniform pain assessment and standardized approaches to pain treatment in children (Reference 17). Pain has often been termed "the fifth vital sign," emphasizing the need for continuous reassessment of hospitalized pediatric patients. Despite these recommendations, pediatric pain management continues to be a challenging field with many barriers because of the developmental changes and pharmacokinetic alterations associated with this heterogeneous population.

Clinical Presentation and Diagnosis

General Assessment Principles

Uniform pain assessment can be very difficult in the pediatric population. Infants may experience nonspecific symptoms of pain with changes in facial expressions and crying; they may also present with autonomic symptoms (e.g., tachycardia, tachypnea), but these symptoms may be associated with their underlying disease state rather than pain by itself (Reference 18). Just like in adults, clinicians should inquire about the character, location, intensity, and duration of painful stimuli in children. Of note, children may not be forthcoming with this information. They may experience a certain level of anxiety with physicians and other health care professionals related to needlesticks, medication injections, and other interventions that they may receive in the clinic, emergency department, or hospital setting. In non-verbal children, it may also be difficult to ascertain whether crying and other behavioral manifestations are associated with pain or other factors such as hunger or fear.

The ability of a child to describe his or her pain varies with age, experience, and cognitive developmental states (Reference 19). In general, clinicians may use self-report, physiologic, and/or behavioral assessments to differentiate between pain and other factors. Because pain is a subjective experience, self-report is generally preferred to make inferences about a patient's pain episodes (Reference 20). However, for non-verbal children or children with cognitive impairment, this may be difficult. Current recommendations call for clinicians to use a child's self-reported pain in conjunction with standardized assessment tools (Reference 20).

Table 1 provides a summary of the most common types of assessment tools. Specific vital sign changes including elevation in heart rate and blood pressure may be used in all ages as an indirect measurement of pain.

Table 1. Summary of Pain Measurement Tools in Children (Adapted from References 18, 19, 25)

Name	Recommended Age Range or Groups	Advantages	Disadvantages
Physiologic measures (e.g., heart rate, blood pressure)	All ages	Useful for nonverbal children	Vital sign changes occur unrelated to pain
Neonatal behavioral/ physiologic scales (e.g., NIPS, NFCS, PIPP)	Premature to full-term infants	Evaluate age-appropriate behavioral and physiologic factors; useful for nonverbal children	Nonspecific in some cases; some are time-consuming; questionable validity in selected patients
Other behavioral/ physiologic scales (e.g., FLACC)	2 months to 7 years	Evaluate age-appropriate behavioral and physiologic factors; useful for nonverbal children	Nonspecific in some cases; some are time-consuming; questionable validity in selected patients
Graphic scale (e.g., color analog scale)	4 years and older	Used for preschool children	Limited utility in children with cognitive impairment or who are color-blind
FACES scale (e.g., Wong-Baker)	3 years and older	Simple scoring tool used for pain discrimination; used for very young preschool children	Children may confuse their emotional states with pain ratings.
Visual Analogue Scale	8 years and older	Straightforward, one-dimensional scoring tool for older children	Limited applicability in children with cognitive impairment
Numerical Rating Scale	7 years and older	Simple scoring tool that can be given verbally or as a written instrument	Application of scores to treatment decisions is inappropriate.
NCCPC-PV	Cognitively impaired children	Validated tool for pain assessment in children with cognitive impairment	Assessment may take substantial time at the bedside to complete (e.g., 10 minutes).

FLACC = Face Legs Arms Cry Consolability Scale; NCCPV-PV = Non-communicating Children's Pain Checklist–Postoperative Version; NFCS = Neonatal Facial Coding System; NIPS = Neonatal Infant Pain Scale; PIPP = Premature Infant Pain Profile.

However, the utility of these markers alone is questionable because of the effects of the child's underlying disease state or other underlying emotional factors (e.g., anxiety, depression). Other more specific pain assessment tools have been developed, but it is important to understand the role of these tools in relation to the child's age and cognitive developmental stages.

Assessment Methods in Pediatric Subgroups

The most common tools used in this population other than physiologic changes are behavioral/physiologic scales. These scales involve the assessment of a variety of behavioral features including crying, facial expressions, body posture/movements, and, in some cases, vital sign changes (e.g., blood pressure, heart rate) (Reference 19). When clinicians evaluate one of the behavioral features alone, they may be unable to assess pain accurately. For example, premature infants and sick full-term infants may be unable to produce an adequate cry when in distress (Reference 19). Many of these scales are available, including the Neonatal Facial Coding System (NFCS), Neonatal Infant Pain Scale (NIPS), and Premature Infant Pain Profile (PIPP). Each scale has been validated in the neonatal population, and each has unique parameters that are evaluated. These scales can be time-consuming, and their utility in intubated neonates is questionable (Reference 19).

Toddlers have a decreased cognitive ability compared with older children and may not have the ability to differentiate between types of pain. As a result, nonverbal behaviors such as facial expressions, limb movements, and crying may be more accurate than their own self-reports (Reference 19). Children older than 3 years will be able to give a good description of the intensity, location, and severity of their pain, whereas verbal toddlers younger than 3 years will often have a decreased ability to do so (References 18, 19). Toddlers may have a limited knowledge of numbers and colors, making it difficult to use certain types of pain assessment tools. Thus, age-appropriate behavioral scales such as the Faces Legs

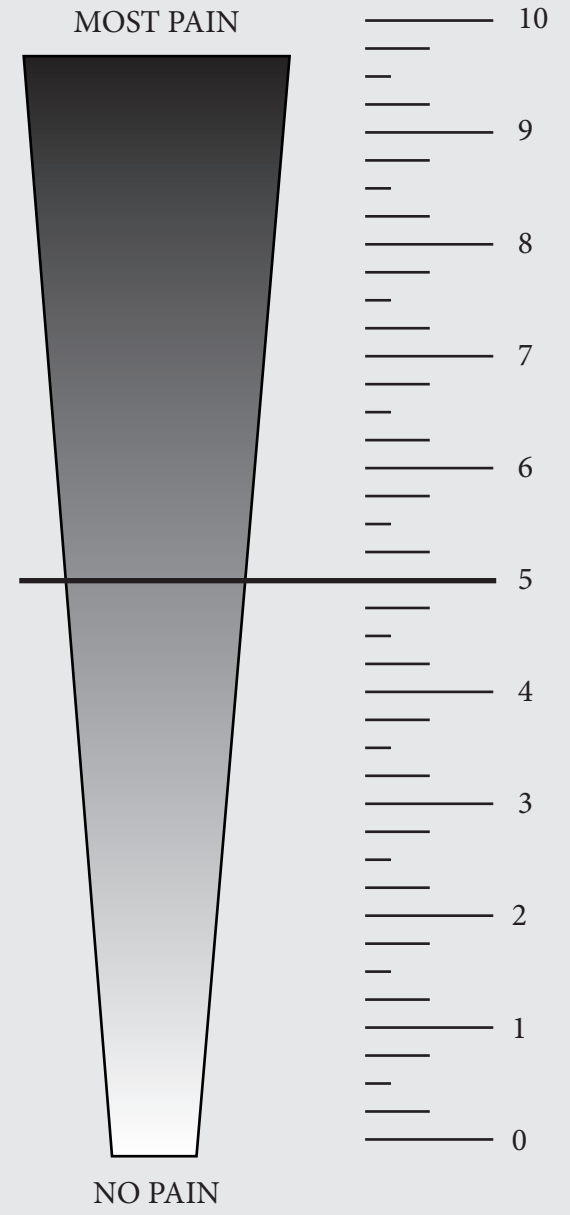


Figure 1. Color Analog Scale (Obtained with permission from Reference 22).

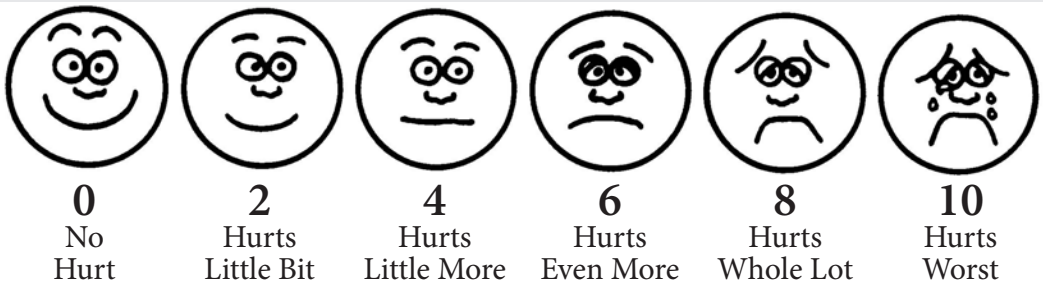


Figure 2. Wong-Baker FACES™ Pain Rating Scale (Obtained with permission from Reference 23).

Activity Cry Consolability Scale (FLACC) have been developed for children as young as 2 months up to 7 years. The FLACC involves a 0- to 10-point scale that evaluates five key indicators, including the face, legs, activity, cry, and consolability (Reference 19). Overall, this scale is relatively easy to use and has been validated in the literature (Reference 21).

Preschool children have an increased ability to articulate and discriminate their pain. By 5 years, most children will be able to rate the severity of their pain (Reference 19). Many different scales have been developed for this age group including the Child Facial Coding System (CFCS), Poker Chip Tool, Graphic Scale, and FACES Pain Scale. Examples of these scales can be found in Figure 1 and Figure 2 (Reference 22). These scales, which can be used in children as young as 4 years, involve the use of color and/or drawings. In general, the higher the number and intensity of color, the more intense the pain. One limitation of this type of tool is its utility for children who are color-blind and/or possess developmental disabilities (Reference 18).

The Wong-Baker FACES Pain Rating Scale is one of the most common tools used by several institutions (Figure 2) (Reference 23). This scale is recommended for children 3 years and older and requires health care professionals to point to each face and describe the corresponding intensity of pain with the corresponding face (Reference 19). Then, the child is asked to point to the face that most accurately describes his or her pain. Although the Wong-Baker scale is one of the most common scales used, one disadvantage of it is that the face associated with "no pain" is the "smiling face." Other similar scales involve the use of a "neutral face" instead of a "smiling face." Investigators compared the Wong-Baker scale versus other types of faces scales (Reference 24). They found that children who saw the smiling face were more likely to report higher pain scores than children who saw the neutral face and suggested that young children may confuse pain ratings with the faces describing different emotional states (Reference 24). For example, an anxious child without a true source of pain may select a face with a corresponding higher pain score because he or she is sad rather than experiencing pain.

School-aged children have an increased ability to describe their pain compared with younger children. In general, they are more concrete thinkers than are preschool children, and they tend to have a better understanding of measurements, quantitative expressions, and facial expressions (References 18, 19). Thus, analog scales such as the Visual Analogue Scale and numerical rating scale (NRS) either use faces or numbers to accurately assess their pain. The Visual Analogue Scale is a one-dimensional pain assessment tool that involves a 100-mm horizontal line with corresponding descriptions of pain (Reference 19). The lower end of the spectrum highlights no pain, whereas the highest point score represents severe pain. Children are asked to mark along the continuum the line that best corresponds to the given pain descriptions. One of the main disadvantages of this tool is that it may have questionable utility in school-aged children with cognitive impairment (Reference 18).

The NRS is another commonly used scoring tool in older children and adults; one example of this scoring tool is its 0 (no pain) to 10 (severe pain) scale. Few studies have evaluated the validity of this scoring tool in children. Recently, the use of the NRS in 113 children ranging from 7 to 16 years old who required hospital admission after surgery for postoperative pain management was evaluated (Reference 25). It was noted that children with NRS scores greater than 4 had good sensitivity and specificity to predict what children needed additional pain medication. However, in children with an NRS score greater than 6, less than one-half of them were somewhat satisfied with their current pain regimen, and another one-fourth of them were very satisfied with their regimen. The investigators concluded that there was a discrepancy in the relationship of higher pain scores and patient satisfaction with their analgesic regimens. In addition, they concluded that the NRS could be used in this population to assess pain but that there might be a limited role in children with the correlation of the NRS for treatment decisions.

Adolescents tend to have the highest capacity to describe their pain, although in front of close family or friends, they may deny the presence of their pain (Reference 19). In fact, they may prefer that friends and family are not present when clinicians assess or discuss their pain. Overall, they generally want the choice to receive interventions for painful procedures, but under certain situations, adolescents may have regression of their developmental ability to cope with their pain (References 19, 20). Most, if not all, pain measurement tools would be acceptable in this population.

For children with cognitive impairment, pain assessment can be very difficult. Children with Down syndrome may not adequately describe the character of their pain (Reference 18). Because the sensory perception in children with autism is different from that in other children, it may be difficult to accurately assess painful stimuli versus other stimuli that may exacerbate their underlying disease (Reference 18). It is imperative that clinicians ascertain the patient's neurologic baseline from the parents/caregivers when a child's self-report is not possible. Recent work has focused on the development of standardized assessment tools in this population. One recent study

sought to validate the Non-communicating Child's Pain Checklist-Postoperative Version (NCCPC-PV), a standardized pain assessment scale in the postoperative period for patients younger than 18 years with cognitive impairment (Reference 26). This scale assesses six domains: vocal sounds, social interaction, facial expressions, general activity, body/limb movements, and physiologic signs. The investigators correlated the score on the NCCPC-PV with that of caregivers and the research team and found good correlation between their assessments. It is extremely important for clinicians to use a multi-professional approach to pain assessment that includes the physician, nursing staff, other allied health care professionals, and parents/caregivers. Recent evidence suggests that the NCCPV-PV is a useful clinical tool to augment clinical assessment in children with cognitive impairment.

Key Point Summary for Pain Assessment

- Pain should be assessed by patient self-report, together with behavioral/physiologic assessments at regular intervals in hospitalized children.
- Several types of behavioral pain assessment tools are available, and each of them may have advantages and disadvantages over another.
- Pain assessment in children with cognitive impairment requires a multidisciplinary approach and can be augmented with validated assessment tools such as the NCCPC-PV.

Treatment

Nonpharmacologic Therapy

Many nonpharmacologic interventions can be used to prevent and treat pain in children. An increasing amount of evidence supports the use of these interventions because they have good safety profiles and very few downsides (References 16, 18). One of the proposed mechanisms of these interventions is that they interfere with pain transmission along the ascending pain pathway by introduction of other excitatory messages (Reference 14). Several different types of health care professionals may be needed to incorporate these therapies. One such health care professional that may be used is the child life specialist; these professionals are trained to employ such nonpharmacologic therapies and educate the parents/caregivers and health care professionals on strategies to reduce and eliminate painful stimuli in children (Reference 16). This education will be needed to ensure the success and implementation of these therapies not only for the patient but also for the other members of the health care team (Reference 16). Everything from the "physical" medical environment to the use of child life specialists can be a useful therapeutic intervention to relieve pain and/or anxiety for children in the emergency department and hospital setting (Reference 16).

In recent years, many nonpharmacologic interventions have been suggested for the neonatal population. These nonpharmacologic interventions are useful to decrease pain and discomfort for neonates during procedures (e.g., heel lancing, adhesive removal, intramuscular/subcutaneous injection, venipuncture, lumbar puncture, suctioning) (References 12, 13). Several of these interventions such as swaddling, facilitated tucking, rocking, pacifier use, and positioning have been validated (Reference 12). Positioning is a useful intervention that allows the infant to adjust himself or herself after a painful procedure. Facilitated tucking is a process by which an infant is wrapped in a blanket and restrained in a tucked position. Practitioners have also focused on targeting environmental factors that may cause neonates pain and anxiety to create a quiet and restful environment. Some neonatal units have taken measures to reduce lighting, decrease the amount of time per day the baby is actually touched, and decrease the volume of alarms and telephones (Reference 12).

The nonpharmacologic therapies in older children can be classified into cognitive, behavioral, and physical interventions. Cognitive therapies include the use of music, guided imagery, distraction, and hypnosis to reduce or eliminate pain (Reference 14). Distraction techniques can include bubbles, therapeutic play, video games, and television. Behavioral techniques can range from breathing exercises to relaxation techniques and may require education for both the provider and patient to be totally effective (Reference 14). Physical nonpharmacologic interventions may also be used; these interventions may involve the use of acupuncture, massage therapy, and application of transcutaneous electrical nerve stimulation (Reference 14). These therapies may be particularly useful for pain in localized regions (Reference 18).

In summary, nonpharmacologic interventions can be very useful for preventing and treating pain in neonates and children. Some children may respond better to nonpharmacologic interventions than others. In addition, certain therapies may not be appropriate for some children and should not be used in place of analgesic agents. A detailed discussion of these interventions is beyond the scope of this chapter, but these interventions have been published elsewhere (References 18, 19).

Pharmacologic Therapy

Pharmacokinetic and Pharmacodynamic Considerations in Children

Developmental Pharmacology Considerations

Clinicians should consider the pharmacodynamic and pharmacokinetic changes that occur with age when selecting not only medication dosing but also the actual analgesic agent. In the first few years of life, significant changes occur in the absorption, distribution, metabolism, and excretion (ADME) of various medications. A complete review of the ADME principles in children appears in the Pediatric Pharmacokinetics chapter, but it is necessary to point out some of these considerations as they pertain to pain medications in infants and children. Neonates have a thinner stratum corneum and greater hydration to the epidermis compared with older children (References 27, 28). As a result, infants may have an excessive exposure of medications administered topically (Reference 29). The application of transdermal medications such as transdermal fentanyl should be avoided in children younger than 2 years because of unpredictability in dosing (Reference 30). Neonates and infants have a diminished capacity to metabolize medications through the hepatic system. Phase 1 and 2 enzymatic reactions including oxidation and glucuronidation, respectively, are significantly delayed in neonates compared with older children. As a result, medication regimens in neonates may need to be altered on the basis of decreased hepatic clearance. For example, several studies have noted inadequate efficacy with morphine in preterm infants (References 31–33). Morphine is metabolized to an active metabolite by glucuronidation. One study suggests these infants have diminished concentrations of morphine-6-glucuronide, the active metabolite of morphine, and elevated concentrations of morphine-3-glucuronide (Reference 31). Elevated concentrations of morphine-3-glucuronide may antagonize the effects of morphine and morphine-6-glucuronide. These enzyme pathways usually mature by about age 6 months (Reference 34). In fact, children who are 2–6 years old often show increased metabolic clearance and may require doses of medications more frequently for a given therapeutic effect.

In addition to knowledge of the developmental changes associated with skin absorption and metabolism, clinicians should be aware of the effects of renal excretion when prescribing certain medications. Specifically, neonates exhibit decreased glomerular filtration and tubular secretion (Reference 34). Morphine-3-glucuronide and morphine-6-glucuronide are both renally excreted, and neurotoxicities like myoclonus could occur in patients with renal insufficiency (Reference 35). As a result, neonates may require an extension of dosing intervals to prevent the accumulation of a given medication and its metabolites.

Pharmacokinetic Alterations in Obese Children

In addition to the developmental changes related to ADME principles in the pediatric populations, other alterations may be noted in obese children. The prevalence of overweight and obese children has increased dramatically during the past 30 years. A study recently found that around 16.9% and 31.7% of children 2–19 years old in 2007–2008 were obese and overweight, respectively (Reference 36). In addition, another study found that one-third of all admissions of patients 5–12 years old during a 6-month period were overweight (Reference 37). A complete review of pediatric obesity may be found in the Pediatric Obesity chapter. Pharmacokinetic alterations have been noted in obese adults, including a higher volume of distribution for lipophilic medications and increased glomerular filtration rates (Reference 38).

There is a paucity of pharmacokinetic studies of obese pediatric patients. Studies of obese adults receiving continuous infusions of fentanyl highlight some possible concerns. Researchers found that optimal dosing of fentanyl continuous intravenous infusions had better correlation with the "pharmacokinetic mass" of the patient rather than an actual, ideal, or adjusted body weight (References 39, 40). The investigators determined the "pharmacokinetic mass" on the basis of observations of the analgesic effect, serum fentanyl concentrations, and fentanyl dose. Results show that as the actual body weight increased, the pharmacokinetic mass increased logarithmically, suggesting an upper limit to the weight by which fentanyl is dosed (Reference 40). There is a concern in obese patients that if fentanyl is dosed on the basis of actual body weight, there is a higher risk of overdosing and adverse events such as oversedation. Until more pharmacokinetic studies have been conducted, it seems reasonable to use the following recommendations for dosing of pain medications in obese children (References 38, 41).

- For children weighing less than 40 kg and younger than 18 years: Use weight-based dosing (i.e., milligram or microgram for single-dose medications and milligrams per kilograms per hour or micrograms per kilograms per hour for continuous intravenous medications).

- For children weighing 40 kg or more:
  - Single-dose medications: Use weight-based dosing unless the patient's dose or dose per day exceeds the recommended adult dose for the indication.
  - Continuous intravenous medications: Avoid weight-based dosing strategies and use adult dosing strategies (i.e., microgram per hour or milligram per hour).

Acute Pain Management

Children who experience acute pain require prompt attention. The World Health Organization (WHO) has developed a useful algorithm, the analgesic ladder, for the management of cancer pain that involves three unique classifications: mild pain, moderate pain, and severe pain (Reference 42). Even though the analgesic ladder was developed to help clinicians treat patients with cancer pain, the principles of this algorithm can be extrapolated to any painful episode, acute or chronic, in children. Non-opioid analgesics are the mainstay of the first stage and should be initiated on a maintenance schedule and titrated to maximum effect. Patients with mild to moderate pain should receive an opioid analgesic with or without a non-opioid analgesic. In general, patients with severe pain should be initiated on scheduled opioid agents. Intermittent doses of opioids can be useful for patients experiencing acute, breakthrough pain, though this strategy often results in a fluctuation of plasma concentrations. Because several opioid agents have relatively short half-lives, the therapeutic benefit may decrease toward the end of the dosing interval, and the patient may experience breakthrough pain. As a result, patients with severe postoperative pain or other painful episodes should receive continuous intravenous opioid infusions or patient-controlled analgesia (PCA) when appropriate. At any stage, clinicians are encouraged to consider the use of adjuvant agents (e.g., benzodiazepines, antidepressants).

Table 2. Non-opioid Analgesic Agents (Adapted from References 44–50)

Medication	Route	Pharmacokinetics	Dose
Acetaminophen	PO	Onset: 0.5 h (PO) t½: 3-7 h (children to neonates)	< 12 Y/O: 10–15 mg/kg/dose q4–6h (max dose NTE > 5 doses/day 75 mg/kg/day or 2.6 g/day) ≥ 12 Y/O: 325–5000 mg q4–6h or 1 g q8h (max dose 3 g/day)
Acetaminophen	RC	Onset: Unknown t½: Unknown	< 12 Y/O: 10–20 mg/kg/dose q4–6h ≥ 12 Y/O: 325–650 mg q4–6h or 1 g q6–8h (max dose 4 g/day)
Acetaminophen	IV	Onset: 0.25 h after a 15-minute infusion t½: 3-7 h (children to neonates)	2–12 Y/O or < 50 kg: 15 mg/kg/dose q6h or 12.5 mg/kg/dose q4h (max single dose NTE 750 mg and max dose per day NTE 75 mg/kg/day or 3.75 g) ≥ 50 kg: 1 g q6h or 650 mg q4h (max single dose NTE 1 g and max dose per day NTE 4 g).
Ibuprofen	PO	Onset: 1–2 h t½: 1–2 h (children)	< 12 Y/O: 4–10 mg/kg/dose q6–8h (max dose 40 mg/kg/day) ≥ 12 Y/O: 200–400 mg q4–6h (max dose 2.4 g/day)
Ketorolac	IV/IM	Onset: 0.5 h t½: 3-6 h (children)	2–16 Y/O or < 50 kg: IM: 1 mg/kg/dose (max dose 30 mg) IV: 0.5 mg/kg/dose (max dose 15 mg); 0.5 mg IV q6h NTE 5 days > 16 Y/O or > 50 kg: 30 mg IV q6h (120 mg/day) NTE 5 days
Naproxen	PO	Onset: 0.5–1 h t½: 8–17 h (children)	2–11 Y/O: 5–7 mg/kg/dose q8–12h > 12 Y/O: 250–500 mg q12h (max dose 1250 mg/day initially; then 1000 mg/day thereafter).
Choline magnesium trisalicylate	PO	Onset: NA t½: 2–3 h (adults)	Based on total salicylate content: Children: 30–60 mg/kg/day divided 3 or 4 times/day Adults: 500 mg–1.5 g 1–3 times/day

h = hour(s); IM = intramuscular; IV = intravenous; max = maximum; NA = not available; NTE = not to exceed; PO = oral; q = every; RC = rectal; t½ = half-life; Y/O = years old.

Non-opioid Analgesics

Non-opioid analgesics represent an attractive option for patients who may be experiencing mild to moderate pain. They have been used in patients with acute and chronic pain in a variety of settings, including children with cancer pain and postoperative pain, and show opioid-sparing effects. In contrast to opioid analgesics, non-opioid analgesics are not associated with respiratory depression, constipation, or urinary retention but may have other risks specific to the individual agents. These agents show a ceiling effect, making their use in patients with moderate to severe pain limited at best. Hence, there is limited efficacy with doses approaching the maximum recommended range but significant risk of toxicity.

This group of agents includes both the nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. The NSAIDs inhibit the cyclooxygenase enzymes' ability to convert arachidonic acid to prostaglandin precursors. Prostaglandins are associated with a wealth of pharmacologic activity including the potentiation of inflammation, protection of the gastrointestinal mucosa, and sensitization of nerves to painful stimuli (Reference 22). Acetaminophen inhibits cyclooxygenase-3, and most experts believe that its main analgesic effects come from inhibiting prostaglandin synthesis in the central nervous system (Reference 43). Unlike NSAIDs, acetaminophen does not inhibit peripheral prostaglandin production, so it is thought not to have any anti-inflammatory activity.

Table 2 includes the most common agents used in an emergency department or inpatient setting. There are no studies comparing the efficacy of these agents in children. In addition, a great degree of patient inter-variability exists between these agents. Therefore, the rationale for choosing one agent over another would include the dosage form, cost, and adverse effect profile.

ACETAMINOPHEN

Acetaminophen represents the most widely used non-opioid analgesic. This agent is available in a variety of formulations including tablets, oral liquid dosage forms (i.e., elixirs, solutions, and suspensions), suppositories, and an intravenous formulation approved in the fall of 2010. For children younger than 12 years, the usual oral dose of acetaminophen is 10–15 mg/kg with a maximum of 75 mg/kg/day or 2.6 g/day (Table 2) (Reference 44). New dosing recommendations for obese children or children older than 12 years were made available in fall 2011 (Reference 50). In the fall of 2011, the maker of Extra Strength Tylenol voluntary changed the labeling for its acetaminophen product from a maximum of 4 g to 3 g/day. The new dosing instructions were developed in an attempt to decrease the incidence of hepatotoxicity secondary to accidental overdoses.

Until late in the spring of 2011, acetaminophen was available in a concentrated solution for young infants (i.e., 100 mg/mL) and in another oral solution for older children (i.e., 32 mg/mL). However, the Consumer Healthcare Products Association released a notice of voluntary removal of the concentrated solution from the market beginning in mid-2011, citing concerns with medication safety of self-care use in the community (Reference 51). In the future, only a single-concentration solution (i.e., 32 mg/mL) will be available. Parents and caregivers of children who receive these products should be educated to use a standardized oral syringe when drawing up and preparing acetaminophen doses for their children because of inaccuracies in parent/caregiver measurement.

Rectal administration of acetaminophen has been used in many different situations for children who may be unable to tolerate oral doses. The recommended doses are found in Table 2. The peak serum concentration is about 2–4 hours (Reference 52). Many sources recommend a loading dose of 20–30 mg/kg/dose to achieve a quicker therapeutic response given that the rectal absorption of this agent is believed to be erratic and slow. Some studies of children in the postoperative period have shown that children may require doses of 25–45 mg/kg to achieve a therapeutic response, but the optimal dosing remains to be determined (Reference 52).

An intravenous formulation of acetaminophen (Ofirmev) has been released. This agent has a U.S. Food and Drug Administration (FDA)-labeled indication for moderate pain and fever in children 2 years and older (Reference 45). Of note, this agent has a quicker onset and higher peak concentration than the oral formulation; however, the total area under the curve is similar to oral administration (Reference 52). Table 2 lists the FDA-labeled dosing. Current studies are investigating the use of this product in children younger than 2 years. In general, the area under the curve of intravenous acetaminophen is higher in this population than in older children and adults. The package insert lists preliminary recommendations for this population, suggesting that a 33% reduction in dose is required for infants to children younger than 2 years, and a 50% reduction in dose is recommended for neonates (Reference 45). Some additional considerations must be noted. A 1000-mg vial of intravenous acetaminophen costs about 10 times as much as oral acetaminophen (Reference 53). Moreover, these vials are intended for single use and short stability after opening (i.e., 6 hours) (Reference 45). Because of these factors, pediatric institutions could experience a significant amount of wastage. Ongoing studies are investigating extended stability with this product. It seems prudent to restrict the use of this product to children who are unable to take anything by mouth for an extended period, patients in the postoperative care setting,

or patients with a contraindication to the rectal administration of medications (i.e., immunocompromised children). In addition, this agent may be considered an alternative to children who have an inadequate response to rectal acetaminophen.

The maximum dosages of acetaminophen products for adults and children are noted in Table 2. The recommendations should especially be noted for children receiving combination opioid analgesic agents because of the propensity for increased hepatic failure with excessive acetaminophen doses. In addition, chronic administration of acetaminophen with doses at or less than the recommended maximum daily doses has been noted to cause hepatotoxicity in healthy adult volunteers (Reference 54).

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

The most common NSAIDs used in the emergency department or hospital setting include ibuprofen, naproxen, choline magnesium trisalicylate, and ketorolac. These agents are attractive because they show analgesic and anti-inflammatory activity. Aspirin is classified as an NSAID; however, this agent should generally be avoided for pain in children younger than 12 years because of concerns about the development of Reye syndrome. The common and maximum doses for these agents are shown in Table 2.

Ibuprofen (Caldolor) and ketorolac are the only intravenous NSAIDs with an FDA-labeled indication for pain in the United States. This agent should not be confused with the other salt form, ibuprofen lysine (NeoProfen, Lundbeck, Deerfield, IL), which is indicated for closure of the patent ductus arteriosus. However, there are currently no studies supporting the use of ibuprofen lysine (NeoProfen) for pain in pediatric patients, and this agent does not have an FDA-labeled indication (Reference 55). Ketorolac is approved for children younger than 2 years for single-dose treatment of 0.5 mg/kg/dose intravenously and 1 mg/kg/dose intramuscularly. Few studies have evaluated the efficacy of several doses of intravenous ketorolac. An observational study reports on 112 children ranging in age from 6 months to 19 years who received usual intravenous doses of 0.5-mg/kg/dose (range 0.17–1.0), most often every 6 hours (Reference 56). Another report describes the use of ketorolac in 53 neonates and infants receiving a multiple dosing regimen (Reference 57). The average dosage regimen included a 0.93 ± 0.14 mg/kg loading dose followed by a maintenance regimen of 0.44 ± 0.09 mg/kg/dose every 6–8 hours. Although the authors did not specifically evaluate efficacy given the retrospective nature of the study, they proposed that the agent provided beneficial analgesic effects in these children after cardiac surgery. Of note, this agent has a black box warning and should not be used for adults or children for more than 5 days because of an increased incidence of adverse events (i.e., gastrointestinal bleeding) (Reference 47).

The NSAIDs are associated with several adverse events that may limit their use in pediatric patients and are associated with an increased incidence of bleeding secondary to their inhibition of platelet aggregation. If a clinician desires to use an NSAID in a patient with thrombocytopenia or increased bleeding, he or she should consider choline magnesium trisalicylate because it has no appreciable effects on platelet aggregation. However, this agent is only available in a liquid preparation, which may not be an acceptable alternative for some patients (Reference 49). Other adverse effects of NSAIDs include nephropathy and gastrointestinal bleeding caused by the inhibition of protective prostaglandins in the kidney and stomach, respectively. Ketorolac has been associated with a significant increase in gastrointestinal bleeding, ulceration, and perforation that appears to be related to duration of therapy and dosing (Reference 47). These agents have been associated with fluid retention and edema, especially in patients with congestive heart failure and cardiac decompensation. However, a recent report suggests this is a safe option in children after cardiac surgery (Reference 57).

Clinicians should consider two other disease states that may preclude the use of NSAIDs. Because NSAIDs inhibit prostaglandin production, children with asthma could experience an increase in leukotriene production, leading to the development of an asthma exacerbation. It is estimated that 2% of children with asthma are intolerant of aspirin, and another 5% of these patients may have a cross-intolerance with other NSAIDs (Reference 58). A diagnosis of asthma alone should not rule out NSAID use in pediatric patients, but this issue does imply that a complete medication history, including a review of allergies, should be taken before an NSAID is prescribed. Another relative precaution of NSAIDs may be for patients with orthopedic injuries. Some animal research suggests that these agents impair bone healing, but there have been conflicting reports in this population (Reference 58). One author recommends that the benefits of these agents outweigh the risk of adverse events, except in patient populations where bone healing may be a significant issue (e.g., patients recovering from posterior or anterior spinal fusions) (Reference 58).

Opioid Analgesics

OVERVIEW

Opioid analgesics represent the mainstay of treatment for moderate to severe pain in children. These agents are available in several different dosage forms. With oral opioids, the onset of activity may be 45 minutes, with peak activity in 1–2 hours (Reference 59). The intravenous

route of administration is favored for patients with an acute onset of severe pain until their pain is under control and for patients unable to take oral medications. Some opioids are available for other routes of administration (e.g., transdermal, oral lozenges); however, these products are generally reserved for chronic pain rather than acute pain.

Overall, the mechanism of opioid analgesia is related to the agonism of μ- and κ-receptors. These receptors, which are coupled with guanine-nucleotide-binding protein (G-protein), modulate nerve activity through these G-proteins. Opioids inhibit the transmission of nerve impulses through the ascending pain pathway in the spinal cord and higher levels in the central nervous system. However, opioids have no effect on pain transmission through the peripheral nervous system. Unlike acetaminophen and NSAIDs, opioids are not associated with a ceiling effect. These agents can be titrated on the basis of clinical effect until significant adverse events, including respiratory depression, occur.

Table 3 lists the equianalgesic doses for the opioid agents together with suggested equianalgesic potencies (References 35, 60–67). Of note, there are significant differences between the potency of the opioid agents. Many different sources provide recommendations for various types of equianalgesic conversions. These conversions are based on potency and on pharmacokinetic parameters of acute versus chronic administration. Clinicians should choose one set of opioid equianalgesic conversions that they are familiar with and use it consistently in their practice setting.

SPECIFIC AGENTS

Intravenous opioids can be delivered by intermittent bolus, continuous infusion, or PCA. Bolus doses may be effective for patients needing immediate relief of pain, but the bolus dose can also be associated with an increase in adverse events. Intermittent dosing has been associated with inadequate pain control as plasma concentrations decrease between doses (References 68, 69). Continuous infusions are often used in patients requiring more steady-state opioid concentrations. This method of delivery has been found extremely effective in the postoperative setting (References 69, 70). Of note about continuous infusions is that patients may become tolerant of the effects of opioids and may require intermittent bolus doses of opioids over time or before painful procedures. Table 3 lists common doses for opioids delivered as continuous intravenous infusions including morphine, fentanyl, and hydromorphone.

Morphine is one of the most frequently prescribed opioid agents in children. It is available in several dosage forms including oral elixirs, tablets, and sustained-release products. Intravenous morphine is the most common opioid administered for intermittent bolus dosing. One important consideration about morphine is related to its metabolism. As mentioned previously, morphine is metabolized by glucuronidation to morphine-6-glucuronide (active metabolite) and morphine-3-glucuronide (inactive metabolite). Several studies have shown that morphine continuous infusions are less efficacious in neonates because of a reduced ability to produce the morphine-6-glucuronide metabolite (References 31–33). Thus, some experts recommend against using this agent for continuous intravenous infusions (Reference 32). Morphine is renally eliminated with a half-life from 1 to 3 hours in older infants and children and from 10 to 20 hours in preterm neonates (Reference 35). With these considerations in mind, see the usual dosage recommendations in Table 3.

Morphine produces a significant degree of hypotension that may limit its use. Many different mechanisms for hypotension have been proposed including histamine-mediated vasodilation, negative chronotropic and inotropic effects on the heart, and a decrease in baroreceptor reflex response (Reference 22). This adverse effect has mainly been implicated in patients who are hemodynamically unstable, but it can also occur with all opioids. In addition, the morphine-mediated histamine release may exacerbate episodes of bronchospasm in patients in status asthmaticus (Reference 71). In these cases, it may be prudent to use alternative opioid agents including hydromorphone and fentanyl.

Hydromorphone is a potent opioid available in both oral and intravenous dosage forms. This agent is generally 5 times more potent than morphine. It may be preferred over morphine for intermittent dosing for patients in renal failure because of its decreased amount of metabolites (Reference 22). Hydromorphone has pharmacologic properties similar to morphine. Table 3 lists the common oral, intermittent bolus, and continuous intravenous infusion doses in children.

Fentanyl is a synthetic opioid that is structurally similar to meperidine. In general, it is thought to be 70–100 times more potent for single-dose administration than intravenous morphine. It is more lipophilic than intravenous morphine and has a quicker onset of action, 30 seconds versus 10 minutes (Reference 61). In addition, fentanyl has a short half-life of about 2 hours in children. With the quick onset and short half-life, this agent is very useful for intubation and other procedures including dressing changes and lumbar puncture.

As a continuous infusion, fentanyl has been found to have a "context-sensitive" half-life of 21 hours secondary to its accumulation in peripheral tissue sites (Reference 72). For patients receiving continuous infusions of fentanyl with acute onset of pain, it would be advisable to administer a bolus dose of fentanyl before increasing the rate of the continuous infusion secondary

Table 3. Opioid Analgesic Agents (Adapted from References 18, 34, 35, 60–67)

Medication	Equianalgesic Dose		Initial IV Dosages		IV/PO Ratio	Initial PO Dosages	
	IM/IV (mg)	PO (mg)	< 40 kg	≥ 40 kg		< 40 kg	≥ 40 kg
Morphine	10	Acute: 60 Chronic 10	Bolus: 0.05–0.2 mg/kg/dose q2–4h (max 15 mg/dose) CI: 0.01–0.03 mg/kg/h	Bolus: 5–10 mg q2–4h CI: 0.8–1.5 mg/h	Chronic: 1:2.5 Acute: 1:6	0.2–0.5 mg/kg/dose q4–6h IR	10–30 mg q4h IR
Hydromorphone	1.5	7.5	Bolus: 0.015 mg/kg/dose q3–6h CI: 0.003–0.005 mg/kg/h	Bolus: 1–2 mg q2–4h CI: 0.3–0.5 mg/h	1:3	0.03–0.08 mg/kg/dose q3–4h (max 5 mg/dose)	2–4 mg q3–4h
Fentanyl	0.1	—	Bolus: 1–2 mcg/kg/dose q1–2h CI: 1–2 mcg/kg/h	Bolus: 25–100 mcg q1–2h CI: 25–100 mcg/h	—	—	—
Methadone	Acute: 10 Chronic: 2–4	Acute: 20 Chronic: 2–4	Bolus: NR CI: NR	Bolus: NR CI: NR	Chronic: 1:2.5 Acute: 1:6	0.1 mg/kg/dose q4 × two or three doses; then 0.1 mg/kg/dose q6–12h (max 10 mg/dose)	5–10 mg q4–12h
Meperidine	75–100	300	Bolus: 0.75–1 mg/kg/dose q3–4h CI: NR	Bolus: 50–100 mg q3–4h CI: NR	1:3	1–1.5 mg/kg/dose q3–4h	50–150 mg q3–4h
Codeine[a]	NR	200	NR	NR	NR	0.5–1 mg/kg/dose q4–6h (max 60 mg/dose)	1 or 2 tablets (30 mg of codeine) q4–6h
Oxycodone[a]	—	15–30	—	—	—	0.05–0.15 mg/kg/dose q4–6h (max of 5 mg/dose of oxycodone)	1 or 2 tablets (5 mg of oxycodone) q4–6h
Hydrocodone[a]	—	30–45	—	—	—	0.2 mg/kg/dose q4–6h	1 or 2 tablets (5 mg of hydrocodone) q4–6h
Tramadol	—	100	—	—	—	—	Immediate-release formulations[b]: 50–100 mg q4–6h (max 400 mg/day) Extended-release formulations[c]: 100 mg/day (max 300 mg/day)

[a]These opioids are available as an oral combination product with acetaminophen. Clinicians should ensure that patients do not exceed 4 g of acetaminophen per day.

[b]Tramadol is available as an immediate-release tablet (50 mg) as Ultram with an FDA-labeled indication for those 17 years and older for moderate to moderate-severe pain. It is also available as an immediate-release orally disintegrating tablet (50 mg) as Rybix with an FDA-labeled indication for age 16 years and older for postoperation, cancer, neuropathic, and low back pain. It is also available as an oral combination product with acetaminophen (Ultracet) for those 18 years and older for short-term (less than 5 days) acute pain management.

[c]Tramadol is available as an extended-release tablet (100, 200, 300 mg) as Ryzolt with an FDA-labeled indication for those 16 years and older and as Ultram ER for those 18 years and older for moderate to moderate-severe pain. It is also available as an extended-release capsule (100, 200, 300 mg) as Con Zip for those older than 18 years with moderate to moderate-severe pain.

CI = continuous intravenous infusion; h = hour(s); IM = intramuscular; IR = immediate-release product; IV = intravenous; NR = not recommended; PO = oral.

to this increased half-life. One adverse event that may limit the use of intermittent doses of fentanyl is chest wall rigidity. A prospective study of 89 premature and term neonates found that the overall incidence was low at 4% (Reference 73). Previous reports have noted that this adverse event occurred with fentanyl doses of 25–50 mcg/kg for patients during anesthetic induction, but this study found that chest rigidity occurred with the rapid administration of doses of 3–5 mcg/kg and greater (Reference 73). Chest wall rigidity can be managed with a dose of intravenous naloxone of 10–40 mcg/kg, administration of a dose of an intravenous neuromuscular blocker before the fentanyl bolus, and/or adjustment of the mechanical ventilator for intubated patients (Reference 73).

Methadone is a long-acting opioid often used for chronic pain, detoxification programs for heroin substance abuse, and treatment of iatrogenic opioid withdrawal in critically ill children. Methadone is metabolized by *N*-demethylation and has an extended half-life of 19 ± 14 hours (range 4–62 hours) in children (Reference 62). It has generally the same potency as morphine, but the peak onset of action for intravenous methadone is 1–2 hours versus 10 minutes for intravenous morphine (Reference 62). Methadone is structurally similar to verapamil and may exert calcium channel blockade (Reference 74). All methadone formulations have been associated with bradycardia, hypotension, and cardiac arrhythmias (Reference 62). One recent report highlighted significant bradycardia with a widened QRS complex in one patient after a methadone continuous intravenous infusion (Reference 74). The rapid administration of an intravenous methadone bolus dose in hemodynamically unstable patients could theoretically increase the likelihood of cardiovascular toxicities. Therefore, clinicians should consider avoiding intravenous methadone administration in children who can tolerate enteral administration of medications.

Meperidine is a synthetic opioid that is less potent, with a shorter duration of action than intravenous morphine. This agent is limited in the acute setting because of adverse events secondary to accumulation of its metabolite, normeperidine (Reference 63). This metabolite is associated with adverse events including seizures, agitation, and hyperreflexia. Risk factors for these adverse events include patients receiving higher doses of meperidine or patients in renal failure (Reference 75). This agent may be reserved for prevention of rigors after the administration of blood products or amphotericin and the treatment of postanesthetic shivering. However, its clinical usefulness for acute pain is limited at best.

Codeine is an opioid available in a combination product for patients with mild to moderate pain. The intravenous route of administration is not routinely recommended secondary to hypotension and vasodilation from histamine release. This agent is metabolized to morphine by cytochrome P450 (CYP) 2D6 and demethylation to morphine (Reference 64). Recent studies suggest that pharmacogenomic differences determine the efficacy of codeine in pain management. One concern is that some children may be "poor metabolizers" because of the decreased activity of the CYP2D6 isoenzyme, resulting in decreased conversion to the active metabolite and decreased analgesic effects (Reference 76). A study investigated the genotype, phenotype, and morphine production in 96 children receiving codeine and diclofenac versus morphine and diclofenac after adenotonsillectomy (Reference 76). The researchers found that 36% of children randomized to codeine and diclofenac had no evidence of conversion to morphine, suggesting these patients have deficiencies in 2D6 isoenzymes. An additional concern is that some patients may be "ultra-fast metabolizers" because of the additional activity of the CYP2D6 isoenzyme, which results in high concentrations of morphine and increased incidence of respiratory depression (Reference 77). Recently, several cases of death in children have been reported because of this pharmacogenomic variation (Reference 78). However, no widespread, clinically useful laboratory test is available to identify these pharmacogenomic variations with the CYP2D6 isoenzyme, and this agent should not be routinely recommended in patients with moderate to severe pain.

Hydrocodone and oxycodone are two other opioids available for oral administration. Structurally, these agents are similar to morphine and are considered more potent than codeine. Oxycodone is the most potent oral opioid agent and is used for moderate to severe pain. Table 3 shows the usual dosage. This agent is available in immediate-release tablets, an oral solution, and a controlled-release product (Reference 65). Hydrocodone is an opioid used for moderate pain control and is available solely in combination products. These combination opioid analgesics are available in oral elixir preparations or tablets (Reference 66). Of note, these agents are typically dosed on a "milligram per kilogram" basis according to the opioid analgesic agent. The FDA has requested that manufacturers of acetaminophen and opioid combination products reduce the acetaminophen content in their dosage forms (Reference 79). Specifically, they have requested that manufacturers reduce the acetaminophen content in these products to 325 mg per tablet, capsule, or other dosage unit to decrease the occurrence of toxicities that have been reported for the past several years.

Despite this change, clinicians should still counsel the parents and guardians of children receiving these medications to halt the use of other acetaminophen-containing products while taking these combination opioid agents.

Tramadol is a centrally acting opiate that binds to μ-opiate receptors to inhibit the ascending pain pathway (Reference 67). This agent also has additional activity beyond its effects with the opioid receptor because it inhibits the reuptake of norepinephrine and serotonin. Tramadol may have a role for some types of pain in the adolescent population. It is available in an immediate-release tablet, an immediate-release orally disintegrating tablet, and an extended-release formulation with FDA-labeled indications for children 16 years and older with moderate-severe pain and other types of pain syndromes, including neuropathic and postoperative pain (Table 3). The use of this agent may be limited in children with underlying seizure disorders because of its ability to lower the seizure threshold. Prescribers should avoid using tramadol in children who are receiving concomitant selective serotonin reuptake inhibitors (SSRIs) because of the potential for serotonin syndrome (Reference 18).

Other dosage forms of opioids are currently on the market. Rectal dosage forms are available for morphine. Fentanyl is available in a transdermal patch, an oral transmucosal lozenge, and a buccal tablet. These agents are preferred for patients with chronic cancer pain (References 30, 80). The transmucosal lozenge is generally avoided in most children because there is a risk they could bite down on the lozenge and receive an unintentional bolus of fentanyl. In general, these medications are not used for the management of acute pain and should not be used in patients who are opioid naive or for patients in the postoperative period.

ADVERSE EVENTS

Several adverse events have been implicated with opioids, but a complete review of these events is beyond the scope of this chapter. Table 4 provides an overview to managing these adverse events (References 22, 81–83). In general, many of the adverse events can be managed by reducing the opioid dose, switching to another opioid agent, or adding another agent. Respiratory depression may be a specific concern in neonates and infants younger than 6 months because of their decreased renal elimination and hepatic immaturity, and they may be at higher risk of significant adverse events including respiratory depression, apnea, and hypoventilation (References 34, 84). As a result, all infants should receive routine pulse oximetry monitoring when administered opioids. Patients with obstructive sleep apnea or those who are opioid naive may also be at increased risk of respiratory depression and should be considered for cardiorespiratory monitoring by end-tidal CO_2 monitoring and/or pulse oximetry (Reference 22).

Other adverse events may be common including constipation, sedation, nausea/vomiting, and pruritus. Of importance, the rate of adverse events depends largely on the agent and dose used for pain control. All patients receiving long-term opioid agents should receive a scheduled bowel regimen to prevent or decrease the incidence of constipation. For patients who are refractory to the first-line agents in Table 4, other alternatives like the addition of low-dose opioid antagonists (e.g., naloxone) have been useful (Reference 22). In patients who experience pruritus, clinicians can consider the administration of oral or intravenous antihistamines to prevent severe itching. One recent review highlighted the potential benefit that opioid antagonists such as low-dose, continuous naloxone infusions may have in patients experiencing a decreased quality of life and comfort associated with profound pruritus (Reference 83). Sedation can be a significant adverse event noted in some patients, especially those with advanced cancer or HIV (human immunodeficiency virus) (Reference 22). In general, sedation can be managed by switching to another opioid agent, but this may not be possible in all patients. Some success has been reported with the use of psychostimulants such as methylphenidate or dextroamphetamine (Reference 22). Clinicians should initiate the lowest dose possible and titrate to effect. Nausea and vomiting can also be a significant complication noted with opioid agents. The addition of antiemetics can be a very helpful strategy to manage this adverse event. Promethazine should be avoided in children younger than 2 years because of the black box warning for respiratory depression in this population. Other alternatives such as 5-HT_3 serotonin receptor antagonists, metoclopramide, and low-dose opioid antagonists may also be useful (Reference 22).

Prolonged use of opioids can also be associated with additional complications that require careful consideration. Some children may experience tolerance; this refers to a decrease in analgesic effect despite a consistent serum plasma opioid concentration (Reference 81). This complication occurs because of cellular changes at the opioid receptor or another receptor distant to it and can be managed by increasing the opioid dose, switching to another agent within its class, or adding another agent to reduce tolerance from occurring (e.g., ketamine, low-dose naloxone) (References 81, 82). In general, patients receiving an extended duration of synthetic opioids like fentanyl are more likely to be at risk because of the higher degree of tolerance associated with these agents versus the tolerance of patients receiving natural opioids like

Table 4. Management of Opioid Adverse Events (Adapted from References 22, 81-83)

Adverse Event	First-line Intervention	Alternative Interventions
Respiratory depression	Reduce opioid dose if possible.	Add low-dose opioid antagonist (e.g., naloxone).
Nausea/vomiting	Reduce opioid dose if possible; add antiemetic agent (e.g., promethazine[a] and/or ondansetron).	Add motility agent (e.g., metoclopramide); alternatively, consider use of low-dose opioid antagonist (e.g., naloxone).
Sedation	Add non-opioid analgesic to limit use of opioids or switch to opioid agent.	Reduce opioid dose or add psychostimulant (e.g., methylphenidate).
Constipation	Add stool softener (e.g., docusate) for all patients, together with stimulant laxative (e.g., bisacodyl).	Add an osmotic laxative (e.g., polyethylene glycol) or consider enema; alternatively, consider use of low-dose opioid antagonist (e.g., naloxone).
Pruritus	Switch to a different opioid agent (e.g., fentanyl); add antihistamine (e.g., diphenhydramine, hydroxyzine).	Alternatively, consider use of low-dose opioid antagonist (e.g., naloxone, nalbuphine).
Tolerance	Increase the opioid dose or switch to a longer-acting agent.	Add a non-opioid analgesic or an agent that prevents or delays tolerance (e.g., α_2-agonist, low-dose naloxone).
Withdrawal	Taper opioid dose slowly or add long-acting opioid agonist (e.g., methadone, extended-release morphine).	Add a α_2-agonist (e.g., dexmedetomidine, clonidine) or gabapentin.

[a]Promethazine for children older than 2 years because of the black box warning for respiratory depression in younger children.

morphine (Reference 82). Extended use of opioids can also result in additional complications including psychological dependence, addiction, and physiologic dependence. Psychological dependence refers to the individual's need for a substance to obtain euphoric effects. Addiction refers to an individual's persistent need to obtain an opioid medication for its euphoric effects, which often involves criminal activity to obtain the agent (Reference 81). Addiction and psychological dependence are rare with acute pain and are topics beyond the scope of this chapter.

Physiologic dependence, more commonly known as opioid abstinence syndrome, can also occur in children who are iatrogenically receiving a prolonged duration of opioids. About 35% to 52% of critically ill infants and children develop withdrawal because of receiving long-term opioids in the intensive care unit setting (Reference 85). Opioid abstinence syndrome symptoms fall into three separate categories: central nervous system irritability (e.g., anxiety, agitation, grimacing, sleep disturbance), gastrointestinal dysfunction (e.g., vomiting, diarrhea), and autonomic dysfunction (e.g., tachypnea, diaphoresis, hypertension) (Reference 85). Several agents have been suggested to treat these symptoms, including α_2-agonists and oral morphine and methadone tapers (Reference 85). It is important for clinicians to have a careful discussion with parents and caregivers to help them understand that children who are experiencing withdrawal from the acute administration of opioids are unlikely to experience psychological dependence.

For children who are discharged on opioids regardless of the indication, clinicians should perform thorough patient education. Analgesics are considered in the top two classes for medication errors in the pediatric population (Reference 37). Because these agents have many serious adverse events, counseling should include not only a complete review of the agent and indication for use, but also proper instruction on the actual administration of the agent. When possible, all parents and caregivers should be given an oral syringe for children receiving liquid dosage forms of the opioid agents. For patients receiving complex taper schedules, parents/caregivers should be provided a schedule including the date of administration, the times of administration, and both the medication dose (in milligrams) and corresponding volume (in milliliters).

Patient- and Nurse-Controlled Analgesia

For children with severe pain, the use of PCA or nurse-controlled analgesia (NCA) can be quite effective. Patients who are administered intravenous intermittent opioid doses can often experience low opioid trough concentrations before their next scheduled dose, leading to increased pain. In addition, the initial administration of a bolus dose can result in an

increased incidence of adverse events such as respiratory depression. With the PCA approach, studies have shown that patients can have similar or even lower pain scores but receive cumulatively fewer opioids than do other children (Reference 22). The PCAs and NCAs involve the use of five components administered through an intravenous delivery pump: initial dose, basal rate, PCA/NCA bolus dose, lockout time between doses (e.g., 5–20 minutes), and maximum opioid dose per hour or per every 4 hours (i.e., depending on the institution's policy) (Reference 86). The three most common agents initiated are morphine, hydromorphone, and fentanyl.

Studies have shown that PCAs can be an effective strategy in children as young as 6 years (Reference 22). Other studies have evaluated the use of PCAs in younger children but have not shown promising results. There have been some concerns that these children may lack the cognitive maturity to understand the relationship between pushing the button on the PCA delivery system and pain relief (Reference 22). Nurse-controlled analgesias can be an alternative for children younger than 6 years, for children with cognitive impairment, or for those who are physically unable to push the button on the delivery system.

In addition to these strategies, parent- or caregiver-controlled analgesia has been suggested for patients with cognitive impairment or for those unable to push the button on the delivery system. This approach is quite controversial and may not be an option at some institutions. Some advocates claim that the parents and caregivers of children know their child better and are thus better able to determine whether they are in pain. This method is thought to benefit children who may be unable to receive prompt attention from their nurse to push the bolus dose on their delivery system in hospitals with a higher patient-to-nurse ratio. The danger with this approach may be of especial concern for children with acute onset of pain who are opiate naive (e.g., postoperative surgery). In such cases, the addition of several bolus doses can result in significant adverse events. As a result, some have restricted the use of this strategy to children with cancer or palliative care and have suggested a thorough education program for parents/caregivers involving pain assessment and an overview of opioids (Reference 22).

Chronic Pain Management

Overview

In addition to the acute pain episodes children experience, there are chronic pain conditions in children that require alternative management, including cancer pain and burn pain. Many of these children may also experience concomitant psychiatric illnesses such as depression, anxiety disorders, and posttraumatic stress disorder that may also affect their pain (Reference 18). Table 5 has some selected adjuvant agents used in the management of chronic pain (References 18, 87–97). Most of the medications do not have an FDA-labeled indication for chronic pain. Dosing information is either extrapolated from adult references, anecdotal case reports, or personal experience. Although these agents are used primarily in the management of chronic pain, the WHO guidelines for pain management clarify that these agents can be used at any stage (i.e., mild, moderate, or severe pain) (Reference 42).

Specific Pain Disorders

NEUROPATHIC PAIN

Neuropathic pain refers to a complex type of chronic pain caused by irregular peripheral and central nervous system activity after the resolution of an injury (e.g., posttraumatic or postsurgical nerve injuries) or inflammatory state (Reference 18). Specific sources of neuropathic pain include solid-organ tumor infiltration of the peripheral nervous system, metabolic disorders, pain after spinal cord injury, and phantom-limb pain (References 18, 22). Adults often present with symptoms including "burning," "tingling," and "stabbing" pain after a hypersensitive response to even the slightest of touch to their skin, called allodynia (Reference 22). Young children may have difficulty describing these symptoms. In these cases, additional tests such as quantitative sensory testing can be conducted to detect sensory abnormalities (Reference 22). Some children and adolescents may also experience a specific type of neuropathic pain called complex regional pain syndrome type I, formerly known as reflex sympathetic dystrophy. This condition is characterized by several different symptoms including allodynia, temperature instability, cyanosis, and swelling and is caused by hyperalgesia in a specific body part (e.g., stomach, esophagus) in patients who have not suffered from a specific nerve injury (References 18, 22).

Managing neuropathic pain in children can be very difficult. In general, patients with neuropathic pain will not respond to opioid analgesics. Table 5 lists some of the most common agents used to treat neuropathic pain. In adults, the most common agents used as first-line treatment include tricyclic antidepressants (TCAs) and antiepileptics. This practice has been expanded to the management of neuropathic pain in children. The two most common TCAs used in children are nortriptyline and amitriptyline. These agents may be especially useful for children who may have insomnia because of their sedative effects. In general, nortriptyline may be preferred over amitriptyline in young children because of the commercial availability

Table 5. Overview of Adjuvant Analgesic Agents (Adapted from References 87–97)

Medication	Indication	Dosing Formulations	Clinical Pearls
Amitriptyline	Neuropathic pain; adjuvant agent for burn pain	Tablets (10, 25, 50, 75, 100, 150 mg)	Obtain ECG before initiating therapy.
Nortriptyline	Neuropathic pain; adjuvant agent for burn pain	Capsule (10, 25, 50, 75 mg); oral solution (2 mg/mL)	Obtain ECG before initiating therapy; preferred TCA in young children
Gabapentin	Neuropathic pain; adjuvant agent for burn pain	Tablet (600, 800 mg); capsule (100, 300, 400 mg); oral solution (50 mg/mL); extemporaneous suspension (100 mg/mL)	Agent with most evidence in neuropathic pain; wide inter-patient variability in dosing
Topiramate	Neuropathic pain (e.g., trigeminal neuralgia)	Tablet (50 mg); extended-release tablets (100, 200, 300 mg); orally disintegrating tablets (50 mg); extemporaneous solution (5 mg/mL)	Cognitive impairment may limit its use in school-aged children.
Fluoxetine	Miscellaneous chronic pain; concomitant depression and anxiety	Capsule[a] (10, 20, 40 mg); oral solution (4 mg/mL); extemporaneous solution (1 mg/mL)	Monitor for drug interactions; avoid abrupt discontinuation.
Escitalopram	Miscellaneous chronic pain; concomitant depression and anxiety	Tablet (5, 10, 20 mg); oral solution (1 mg/mL)	Monitor for drug interactions; avoid abrupt discontinuation.
Diazepam	Decrease anxiety	Tablets (2, 5, 10 mg); oral solutions (1, 5 mg/mL)	Concentrated diazepam solution contains 19% ethanol; prolonged half-life; relies heavily on hepatic metabolism
Lorazepam	Decrease anxiety	Tablets (0.5, 1, 2 mg); oral solution (2 mg/mL)	Preferred benzodiazepine for acute pain management
Clonidine	Decrease the need for additional opioids; adjuvant agent for burn pain	Tablets (0.1, 0.2, 0.3 mg)[b]; extended-release tablets (0.1 mg); extemporaneous suspension (0.1 mg/mL)	Must be tapered off before discontinuation to avoid withdrawal symptoms

ECG = electrocardiogram; TCA = tricyclic antidepressant.
[a]Also available in tablets (10, 20 mg) as Sarafem with an FDA-labeled indication for premenstrual dysphoric disorder.
[b]Also available in a 0.1-mg extended-release tablet (Kapvay) for children with ADHD and a 0.17-mg extended-release tablet (Nexiclon XR) and 0.09-mg/mL extended-release oral suspension (Nexiclon XR) with an FDA-labeled indication for hypertension in adults.

of an oral solution. Both of these agents have the potential to cause QT prolongation (References 89, 90). Clinicians should perform a thorough physical and family history for cardiac arrhythmias, heart disease, and syncope before these agents are initiated (Reference 18). A baseline electrocardiogram should be conducted on all children (Reference 22). Additional QT monitoring should be considered in patients who require additional increases in dosing for their pain. Children who develop a corrected QT interval greater than 445 milliseconds should be referred to a pediatric cardiologist (Reference 18). Because of the potential toxic effects of these medications, some experts have suggested that clinicians prescribe no greater than a 30-day supply of them to ensure that only limited adverse events occur in children who may attempt suicide. When these agents are discontinued, clinicians should gradually taper the doses of the agents to prevent discontinuation syndrome (i.e., symptoms including agitation, sleep disturbances, and gastrointestinal complications) (Reference 18).

Several antiepileptics have been used to treat neuropathic pain. Table 5 lists two antiepileptics that have been used. The most available evidence is with gabapentin, but of note, no randomized controlled trials have compared the use of one antiepileptic over another (Reference 22). Gabapentin has a favorable safety profile with less somnolence than other antiepileptics and is available in different dosage formulations for the pediatric population (Reference 91). One

important consideration with this agent is that the dosing for neuropathic pain is very patient-specific, and it is difficult to make conclusive recommendations on the dosing range for this indication. Topiramate is another antiepileptic that has been used in selected patients with trigeminal neuralgia (Reference 18). One particular concern with this agent is the potential for cognitive impairment. Children with this adverse event may have speech problems, memory difficulties, and significant problems concentrating, rendering this agent not useful for school-aged children (Reference 92). One additional adverse event that should be monitored in patients receiving topiramate is weight loss. This adverse event may be especially difficult in children receiving palliative care who already may have difficulty in receiving adequate nutrition. Other antiepileptics have been used including valproic acid and carbamazepine, but the adverse effect profiles of these agents often limit the routine use for this indication in children (Reference 18).

Other antidepressants may be effective adjuvant agents in children experiencing neuropathic pain. The SSRIs have shown some effect in adults to decrease various types of pain episodes (Reference 18). These agents may be especially useful in children with concomitant anxiety and depression in addition to chronic pain. Table 5 lists two of the SSRIs with an FDA indication for depression in the pediatric population (References 93, 94). Alternatively, venlafaxine and duloxetine have also shown some promise in the management of chronic pain. These agents inhibit the release of norepinephrine and serotonin and may have some direct effect on antagonizing selected pain receptors (Reference 18). In children with chronic pain and concomitant depression, the SSRIs, venlafaxine, and duloxetine may be preferred over TCAs because of the difference in their adverse event profiles. There are special concerns to note, however. Venlafaxine is associated with hypertension and orthostatic hypotension, and for this reason, children receiving this agent should receive routine blood pressure monitoring (Reference 18). The SSRIs may be associated with serotonin syndrome in children receiving concomitant agents such as tramadol and trazodone (Reference 18).

CANCER PAIN

Children with cancer experience pain from many different sources. For example, children with a newly diagnosed solid-organ tumor may experience severe pain as a symptom on initial presentation. These tumors can cause significant pain because of infiltration of the viscera, bone, and nerves (Reference 22). Children with hematologic malignancies such as leukemia and lymphoma can also experience infiltration of malignant cells into the viscera and bone marrow and also can present with splenic and hepatic distention (Reference 22). Other children may experience pain from many different etiologies including severe mucositis, distress from painful diagnostic or therapeutic procedures, or pain associated with metastasis to other organs (e.g., bone, lungs).

Mucositis can be a difficult source of acute but also chronic pain in children with cancer. This complication can occur as the result of high-dose chemotherapy or radiation. A complete review of this topic is beyond the scope of this chapter. In general, the mainstay of treatment is preventive care, with good oral hygiene performed to ensure removal of loose tissue and to keep the mucosa moist. This can be accomplished with saline, chlorhexidine, or hydrogen peroxide mouth rinses (Reference 98). For patients experiencing mild cases of mucositis, treatment involves topical therapies consisting of sucralfate, magnesium hydroxide, and viscous lidocaine (Reference 98). For patients with more profound pain, opioid agents should be considered. In patients undergoing bone marrow transplantation in which mucositis may be a profound problem, children may require the use of PCAs to control their pain (Reference 22).

The management of advanced cancer pain in children is very difficult and involves the use of pharmacologic and nonpharmacologic approaches. In such cases, the goal should be to keep the patient comfortable and optimize their quality of life. The NSAIDs should be initiated for children experiencing bone pain. Choline magnesium trisalicylate should be first-line therapy in children with profound thrombocytopenia. Scheduled opioids should be initiated for severe pain. In children able to take solid dosage forms, sustained-release or extended-release agents should be initiated, together with an immediate-release product for breakthrough pain. Methadone oral solution may be a suitable alternative in children who are unable to swallow tablets because of its long half-life. Transdermal fentanyl may also be an option in children older than 2 years. The doses of these agents should be escalated on the basis of the patient's response, keeping in mind that both tolerance and the disease itself will have a profound impact on a child's opioid requirement. In refractory cases, PCAs should be considered and titrated to effect until these agents can be switched to a more acceptable long-term alternative. Clinicians should keep in mind that the opioid adverse events might be the rate-limiting step in escalating a child's dose. As a result, they should use the strategies listed in Table 4 and consider using an adjuvant agent in Table 5 to reduce the incidence of these adverse events. It has been estimated that 90% of children with advanced cancer will respond to gradual escalation in their opioid therapy (Reference 18). However, another 5% of children may require more than a 100-fold increase in their opioid

dose and the use of alternative approaches to pain management including intrathecal administration of anesthetics and opioids, agents targeted at neuropathic pain (e.g., gabapentin), or sedative agents (Reference 22). Nonpharmacologic interventions such as spiritual care and massage therapy should also be considered for children receiving palliative care.

BURN PAIN

Children with burn injuries will also experience both acute and chronic pain. Thermal, electrical, and chemical burns are common in children younger than 10 years (Reference 87). All children with burn injuries will experience pain, no matter the type or severity of the injury. If this pain is untreated in children, they may experience nonadherence to their treatment therapies and have delayed wound healing (Reference 88). They may also develop concomitant psychiatric disease states such as posttraumatic stress disorder because of the untreated pain (Reference 88). Children with acute burn pain may experience background or continuous pain as well as pain associated with procedures (Reference 87). Although the continuous or background pain can be alleviated with scheduled analgesics, the management of procedural pain (e.g., associated with dressing changes) may be difficult to assess. Clinicians may have a difficult time identifying that the procedure itself is a source of a child's pain; thus, many children may have a source of untreated pain during these periods (Reference 88).

Once the burn injuries are healed, children with these injuries may experience chronic pain, often because of neuropathic pain (Reference 88). In such cases, opioid and non-opioid agents will not be entirely effective in diminishing pain. Antidepressants and antiepileptics are useful treatments in these situations. Evidence has suggested that gabapentin has several roles in the management of burn pain. This agent has been shown to decrease the hyperalgesia associated with acute injury and has shown some positive impact in children with neuropathic pain (Reference 87). In addition, gabapentin has been a useful agent to inhibit the management of refractory pruritus in children after burn injuries (Reference 87).

Anxiety can play a major role in the underlying pain that children face after a burn injury. They may especially be anxious before procedures, and treating their anxiety can decrease their anticipatory anxiety before the procedure. Anxiolytic agents have also been shown to reduce opioid requirements and may have a role in decreasing opioid tolerance (Reference 88). As a result, clinicians have often used benzodiazepines as an adjuvant therapy in burn victims. Table 5 lists two specific benzodiazepines used in maintenance therapy. Diazepam has a long and variable half-life in children that ranges from 15 to 95 hours (Reference 95). It undergoes extensive hepatic metabolism to two active metabolites. Lorazepam has a shorter half-life and is primarily metabolized by glucuronidation to an inactive metabolite (Reference 96). Lorazepam may be preferred to diazepam in patients with burn injuries who may have hepatic or renal insufficiency to avoid the accumulation of active metabolites.

Central α_2-agonists such as clonidine may also be a useful approach to alleviating acute and chronic pain associated with burn injuries. Children with acute burn injuries may require significant escalation in their opioid doses to achieve analgesic effect because of rapidly developing tolerance. In such cases, patients may develop an increased incidence of adverse events, limiting the utility of opioids for chronic pain (Reference 87). These agents work to augment the descending pain pathway and thus possess anxiolytic, sedative, and analgesic properties (Reference 88). Studies have noted that these agents can have an opioid-sparing effect in certain types of pain episodes (Reference 87). Clonidine is available as an enteral formulation and as a transdermal patch. Of note, this agent can also be compounded as an extemporaneous formulation that can be suitable for young children (Table 5) (Reference 97). The transdermal patch may be suitable in some patients. The lowest dosage form is 0.1 mg, and this dose may exceed the recommended initial dose per kilogram for young children. Some individuals have suggested that these patches be cut into smaller patches; however, this practice is not encouraged because of difficulty in obtaining consistent pharmacokinetic concentrations (Reference 85). Dexmedetomidine is another commercially available α_2-agonist. This agent is 6–8 times as potent as clonidine; however, it is only available as an intravenous agent and would not be appropriate for long-term administration (Reference 85). Special care must be taken in children who discontinue these agents. Withdrawal symptoms are common and can include rebound hypertension, irritability, and agitation if they are tapered off too quickly (Reference 85).

Procedural Pain Management

Other non-opioid analgesics may be used for localized administration in children in the emergency department or hospital setting. These agents may be used for many different indications including suture of lacerations, needle procedures, placement of an intravenous line, and prevention of pain associated with laboratory draws (References 99, 100). The following are recommendations for medications for minor procedures and suture/laceration repair in the emergency department and inpatient settings.

Lidocaine-Based Agents

Several lidocaine-based agents have been used for minor procedures for placement of intravenous lines and prevention of pain with blood draws including EMLA, LMX_4, lidocaine iontophoresis, Synera, and the J-Tip needless injection system. The drug EMLA (Abraxis Pharmaceutical Products, East Schaumburg, IL) is a eutectic mixture available in a cream formulation of local anesthetics including 2.5% lidocaine and 2.5% prilocaine. This drug is recommended to be applied to a clean, intact area of the skin about ½ inch past the area needed for anesthesia and covered with an occlusive dressing for about 1 hour before venipuncture (Reference 101). This formulation has an FDA-labeled indication with dosing based on age and weight (Reference 102). However, one source notes that the application of EMLA may be necessary for up to 2–3 hours before intramuscular injection for full anesthesia efficacy (Reference 102). Because of the risk of methemoglobinemia, EMLA should be avoided in neonates with a gestational age younger than 37 weeks (Reference 101).

The drug LMX_4 (Ferndale Laboratories, Ferndale, MI) is a 4% topical lidocaine formulation manufactured in an encapsulated lipid layer for greater dermal absorption. It is available over the counter in the United States and is recommended for children 2 years and older (References 102, 103). This product has significant advantages because it is available over the counter for patients with chronic illness who may require frequent trips to the emergency department and because it has a fast onset of activity (i.e., 15–30 minutes for LMX_4 vs. 1 hour for EMLA).

Another formulation that may be used for minor procedures is Numby Stuff (Iomed, Salt Lake City, UT). This product contains 2% lidocaine with 1:100,000 epinephrine, which is delivered through an electrical current called iontophoresis (Reference 104). A prospective randomized trial comparing the use of lidocaine iontophoresis with EMLA in 100 preoperative pediatric patients found a significant difference in the time to accomplish anesthesia, 13 minutes versus 60 minutes ($p<0.001$) (Reference 105). This product has a faster onset than EMLA and LMX_4 because it achieves anesthesia efficacy 10–20 minutes after administration. In addition, it provides a much broader area of action than EMLA and LMX_4, with 8–9 mm in duration (Reference 22). Clinicians should note that the Numby Stuff delivery system might be limited in some patients because of discomfort on administration (Reference 106).

Another product, Synera, was recently approved for children 3 years and older for superficial venous access and dermatologic procedures (e.g., shave biopsy of skin and skin excision) (Reference 107). Synera (ZARS Pharma, Salt Lake City, UT) is a combination patch consisting of lidocaine 70 mg and tetracaine 70 mg (Reference 107). This unique disposable patch is composed of an oxygen-activating system to enhance the absorption of the active ingredients through the stratum corneum. After it is removed from its package, its level of heating reaches a maximum skin temperature of 40°C or less (Reference 108). This agent has an onset time of 20 minutes, and ideally, it should be applied 20–30 minutes before procedures. Of importance, several patches should be applied simultaneously or in immediate succession, and the Synera patch should not be applied to broken or non-intact skin (Reference 107).

In 2001, a needle-free injection of lidocaine, the J-Tip needleless injection system (National Medical Products, Irvine, CA), was introduced to the market. This agent is a disposable, needle-free injection device that uses pressurized carbon dioxide to deliver either 0.25 mL or 0.5 mL of lidocaine into subcutaneous skin (Reference 109). This product, a delivery system, must be filled in the pharmacy with typically 1% to 2% buffered lidocaine powder (Reference 109). The product is operated by pressing the device firmly against the skin where the procedure is to take place. Then, subsequently pressing the lever on the device begins the delivery of the lidocaine within seconds and results in an onset of analgesia in 1–3 minutes (Reference 108).

The American Academy of Pediatrics (AAP) Committee on Pediatric Emergency Medicine and Section on Anesthesiology and Pain Medicine has provided recommendations on the role of selected topical agents for procedural pain (Reference 16). They recommend that EMLA and LMX_4 be used interchangeably in many different settings for painful procedures including lumbar puncture, joint aspiration, and abscess drainage (Reference 16). This committee did not specifically address Numby Stuff, Synera, or the J-Tip needle-free injection system. It is difficult to make evidence-based decisions between these agents because there are few clinical trials comparing them. All of these agents have a different onset of action, a variance in cost, and different delivery mechanisms. For pain prevention with procedures, the committee recommended that the lidocaine-based agents be administered as soon as possible to the affected area to ensure adequate anesthetic effect. One important consideration is that, regardless of the lidocaine-based agent used, it will not provide complete pain relief. Other agents like benzodiazepines and opioids may also have to be administered to complete these procedures. Relative contraindications to the products include allergies to amide anesthetics, non-intact skin, and recent administration of a sulfonamide antibiotic (i.e., EMLA only).

Miscellaneous Agents

For patients requiring other minor procedures including suture and laceration repair, clinicians may use a combination of topical anesthetics/vasoconstrictor combinations

such as lidocaine, epinephrine, and tetracaine (LET). The exact formulation of LET may differ from institution to institution according to the recipe of the pharmacy department in the particular institution. This product has been noted to achieve anesthesia for wound suture repair in 20–30 minutes (Reference 110). The AAP recommends that a maximum dose of 3 mL of LET is indicated for lacerations of the head, neck, extremities, or trunk less than 5 mm in duration. The use of LET is contraindicated in patients who may have an allergy to one of the amide anesthetics, for wounds greater than 5 mm in duration, or for wounds in the ear and genitalia. Of note, the maximum dose of lidocaine administered without epinephrine is 4 mg/kg and, with epinephrine, is 7 mg/kg (Reference 22). Some experts also recommend that intravenous diphenhydramine could be used if a patient receives greater than the maximum dose of lidocaine or LET because of intravenous diphenhydramine's partly local anesthetic effects (Reference 22).

Another unique pharmacologic agent that has been used for minor procedures is vapocoolant spray. This product works by rapidly cooling the skin, with the goal of slowing the initiation and conduction of nerve impulses (Reference 108). Gebauer's Ethyl Chloride (Gebauer's Pain Ease, Cleveland, OH) is recommended for venipuncture and minor procedures (Reference 111). This agent works immediately, but its duration of action is 15 seconds. Gebauer's Pain Ease should be sprayed for 4–10 seconds continuously and at no greater than 7 inches away from the skin (Reference 111). Experts state that if this agent is used, it may take two providers to perform the procedure, with one professional to administer the agent and the other one to perform the procedure (Reference 108). Some children may not tolerate the cooling sensation and may have increased anxiety and perceived pain from the administration of this agent alone. With the availability of other agents for minor procedures, the use of the agents has diminished (Reference 108).

Oral sucrose solutions may be considered for infants for prevention of pain with minor procedures. Sucrose solutions have been associated with a decrease in the production of painful stimuli from heel sticks and venipunctures in neonates (Reference 112). Several institutions have adopted compounded formulations of sucrose. Two commercially available products are available on the market, Sweet-Ease (Children's Medical Ventures, Norwell, MA) and Toot Sweet (Natus Medical, San Carlos, CA). A study found significant analgesic activity with sucrose combined with the use of a pacifier in neonates (Reference 113). Therefore, the AAP recommends that sucrose solutions be administered to infants younger than 6 months and be used in combination with a pacifier and administered no more than 2 minutes before starting a procedure (Reference 16).

Conclusions

Pediatric pain management remains a definite challenge for health care professionals. Many differences exist between the assessment and management of pain in children versus adults. Each institution should ensure that pain is assessed on a routine basis with a standardized approach. Several nonpharmacologic interventions are available that should be used in conjunction with pharmacologic treatment. Pharmacists definitely need to be involved in the multidisciplinary pain management in children. As pharmacists, we can play a role in the selection of the appropriate medication for the specific type of pain, monitoring of adverse events, and provision of recommendations for managing these adverse events. In addition, all pharmacists should be involved with the education of parents/caregivers and the patients themselves to ensure that they understand the indication for each pain medication and understand how to safely administer these medications.

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