Children are not just “little adults,” and lack of data on important pharmacokinetic and pharmacodynamic differences has led to several disastrous situations in pediatric care.

Variations in absorption of medications from the gastrointestinal tract, intramuscular injection sites, and skin are important in pediatric patients, especially in premature and other newborn infants.

The rate and extent of organ function development and the distribution, metabolism, and elimination of drugs differ not only between pediatric versus adult patients but also among pediatric age groups.

The effectiveness and safety of drugs may vary among age groups and from one drug to another in pediatric versus adult patients.

Concomitant diseases may influence dosage requirements to achieve a targeted effect for a specific disease in children.

Use of weight-based dosing of medications for obese children may result in suboptimal drug therapy.

The myth that neonates and young infants do not experience pain has led to inadequate pain management in this pediatric population.

Special methods of drug administration are needed for infants and young children.

Many medicines needed for pediatric patients are not available in appropriate dosage forms; thus, the dosage forms of drugs marketed for adults may require modification for use in infants and children, necessitating assurance of potency and safety of drug use.

The pediatric medication-use process is complex and error prone because of the multiple steps required in calculating, verifying, preparing, and administering doses.

### INTRODUCTION

Remarkable progress has been made in the clinical management of disease in pediatric patients. This chapter highlights important principles of pediatric pharmacotherapy that must be considered when the diseases discussed in other chapters of this book occur in pediatric patients, defined as those younger than 18 years. Newborn infants born before 37 weeks of gestational age are termed premature; those between 1 day and 1 month of age are neonates; 1 month to 1 year are infants; 1 to 11 years are children; and 12 to 16 years are adolescents.

This chapter covers notable examples of problems in pediatrics, pharmacokinetic differences in pediatric patients, drug efficacy and toxicity in this patient group, and various factors affecting pediatric pharmacotherapy. Specific examples of problems and special considerations in pediatric patients are cited to enhance understanding.

Infant mortality up to 1 year of age has declined from 200 per 1,000 births in the 19th century to 75 per 1,000 births in 1925 and to 6.14 per 1,000 births in 2010. This success has resulted largely from improvements in identification, prevention, and treatment of diseases once common during delivery and the infancy period. Although most marketed drugs are used in pediatric patients, only one fourth of the drugs approved by the U.S. Food and Drug Administration (FDA) have indications specific for use in the pediatric population. Data on the pharmacokinetics, pharmacodynamics, efficacy, and safety of drugs in infants and children are scarce.

Lack of this type of information led to disasters such as gray baby syndrome from chloramphenicol, phocomelia from thalidomide, and kernicterus from sulfonamide therapy. Gray baby syndrome was first reported in two neonates who died after excessive doses of chloramphenicol (100–300 mg/kg/day); the serum concentrations of chloramphenicol immediately before death were 75 and 100 mcg/mL (75 and 100 mg/L; 232 and 309 μmol/L). Patients with gray baby syndrome usually have abdominal distension, vomiting, diarrhea, a characteristic gray color, respiratory distress, hypotension, and progressive shock.

Thalidomide is well known for its teratogenic effects. Clearly implicated as the cause of multiple congenital fetal abnormalities (particularly limb deformities), thalidomide also can cause polyneuropathy, nerve damage, and mental retardation. Isotretinoin (Accutane) is another teratogen. Because it is used to treat severe acne vulgaris, which is common in teenage patients who may be sexually active but not willing to acknowledge that activity to healthcare professionals, isotretinoin has presented a difficult problem in patient education since its marketing in the 1980s.

Kernicterus was reported in neonates receiving sulfonamides, which displaced bilirubin from protein-binding sites in the blood to cause hyperbilirubinemia. This results in deposition of bilirubin in the brain and induces encephalopathy in infants.

Another area of concern in pediatrics is identifying an optimal dosage. Dosage regimens cannot be based simply on body weight or surface area of a pediatric patient extrapolated from adult data. Bioavailability, pharmacokinetics, pharmacodynamics, efficacy, and safety information can differ markedly between pediatric and adult patients, as well as among pediatric patients, because of differences in age, organ function, and disease state. Significant progress has been made in the area of pediatric pharmacokinetics during the past 2 decades, but few such studies have correlated pharmacokinetics with the outcomes of efficacy, adverse effects, or quality of life.

Several additional factors should be considered in optimizing pediatric drug therapy. Many drugs prescribed widely for infants and children are not available in suitable dosage forms.
For example, extemporaneous liquid dosage forms of amiodarone, captopril, omeprazole, and spironolactone are prepared for infants and children who cannot swallow tablets or capsules, and injectable dosage forms of aminophylline, methylprednisolone, morphine, and phenobarbital are diluted to accurately measure small doses for infants. Alteration (dilution or reformulation) of dosage forms intended for adult patients raises questions about the bioavailability, stability, and compatibility of these drugs. Because of low fluid volume requirements and limited access to IV sites, special methods must be used for delivery of IV drugs to infants and children. As simple as it may seem, administration of oral drugs to young patients continues to be a difficult task for nurses and parents. Similarly, ensuring adherence to pharmacotherapy in pediatric patients poses a special challenge.

Finally, the need for additional pharmacologic or therapeutic research brings up the issue of ethical justification for conducting research. Investigators proposing studies and institutional review committees approving human studies must assess the risk-to-benefit ratio of each study to be fair to children who are not in a position to accept or reject the opportunity to participate in the research project.

Enormous progress in pharmacokinetics has been made in pediatric patients. Two factors have contributed to this progress: (a) the availability of sensitive and specific analytic methods to measure drugs and their metabolites in small volumes of biologic fluids and (b) awareness of the importance of clinical pharmacokinetics in optimization of drug therapy. Absorption, distribution, metabolism, and elimination of many drugs are different in premature infants, full-term infants, and older children, and this topic is discussed in detail in the next few sections.

**ABSORPTION**

**Gastrointestinal Tract**

Two factors affecting the absorption of drugs from the gastrointestinal tract are pH-dependent passive diffusion and gastric emptying time. Both processes are strikingly different in premature infants compared with older children and adults. In a full-term infant, gastric pH ranges from 6 to 8 at birth but declines to 1 to 3 within 24 hours. In contrast, gastric pH remains elevated in premature infants because of immature acid secretion. In premature infants, higher serum concentrations of acid-labile drugs, such as penicillin, ampicillin, and nafcillin, and lower serum concentrations of a weak acid such as phenobarbital can be explained by higher gastric pH. Because of a lack of extensive data comparing serum concentration–time profiles after oral versus IV drug administration, differences in the bioavailability of drugs in premature infants are poorly understood. Although little is known about the influence of developmental changes with age on drug absorption in pediatric patients, a few studies with drugs (e.g., digoxin and phenobarbital) and nutrients (e.g., arabinose and xylose) have suggested that the processes of both passive and active transport may be fully developed by approximately 4 months of age. Little is known about the development and expression of the efflux transporter P-glycoprotein and the intestinal drug-metabolizing enzymes and their impact on drug absorption and bioavailability in infants and children.

Studies have shown that gastric emptying is slow in premature infants. Thus, drugs with limited absorption in adults may be absorbed efficiently in premature infants because of prolonged contact time with gastrointestinal mucosa.

**Intramuscular Sites**

Drug absorption from an intramuscular site may be altered in premature infants. Differences in relative muscle mass, poor perfusion to various muscles, peripheral vasomotor instability, and insufficient muscular contractions in premature infants compared with older children and adults can influence drug absorption from the intramuscular site. The net effect of these factors on drug absorption is impossible to predict; phenobarbital has been reported to be absorbed rapidly, whereas diazepam absorption may be delayed. Thus, intramuscular dosing is used rarely in neonates except in emergencies or when an IV site is inaccessible.

**Skin**

Percutaneous absorption may be increased substantially in newborns because of an underdeveloped epidermal barrier (stratum corneum) and increased skin hydration. Furthermore, because the ratio of total (BSA) to total body weight is highest in the youngest group, the relative systemic exposure of topically applied drugs, including corticosteroids, may be higher in infants and young children than in adults. The increased exposure can produce toxic effects after topical use of hexachlorophene soaps and powders, salicylic acid ointment, and rubbing alcohol. Interestingly, a study has shown that a therapeutic serum concentration of theophylline can be achieved for control of apnea in premature infants less than 30 weeks' gestation after topical application of gel containing a standard dose of theophylline. Use of this route of administration may minimize the unpredictability of oral and intramuscular absorption and the complications of IV drug administration for certain drugs. A transdermal patch formulation of methylphenidate has been approved for use in children 6 to 12 years of age for treatment of attention-deficit/hyperactivity disorder (ADHD). The patch can be applied once daily and can remain on during normal activities such as bathing, swimming, and exercising.

**Distribution**

Drug distribution is determined by the physicochemical properties of the drug itself (pKₐ, molecular weight, partition coefficient) and the physiologic factors specific to the patient. Although the physicochemical properties of the drug are constant, the physiologic functions often vary in different patient populations. Some important patient-specific factors include extracellular and total body water, protein binding by the drug in plasma, and presence of pathologic conditions modifying physiologic function. Total body water, as a percentage of total body weight, has been estimated to be 94% in fetuses, 85% in premature infants, 78% in full-term infants, and 60% in adults. Extracellular fluid volume also is markedly different in premature infants compared with older children and adults; the extracellular fluid volume may account for 50% of body weight in premature infants, 35% in 4- to 6-month-old infants, 25% in 1-year-old children, and 19% in adults. This conforms to the observed gentamicin distribution volumes of 0.48 L/kg in neonates and 0.20 L/kg in adults. Studies have shown that the distribution volume of tobramycin is largest in the most premature infants and decreases with increases in gestational age and birth weight of the infant.

Binding of drugs to plasma proteins is decreased in newborn infants because of decreased plasma protein concentration, lower binding capacity of protein, decreased affinity of proteins for drug binding, and competition for certain binding sites by endogenous compounds such as bilirubin. The plasma protein binding of many drugs, including phenobarbital, salicylates, and phenytoin, is significantly less in the neonate than in adults. The decrease in plasma protein binding of drugs can increase their apparent volumes of distribution. Therefore, premature infants require a larger loading dose than older children and adults to achieve a therapeutic serum concentration of drugs such as phenobarbital and phenytoin.
The consequences of increased concentrations of free or unbound drug in the serum and tissues must be considered. Pharmacologic and toxic effects are related directly to the concentration of free drug in the body. Increases in free drug concentrations may result directly from decreases in plasma protein binding or indirectly from, for example, drug displacement from binding sites. Increased mortality from the development of kernicterus secondary to displacement of bilirubin from albumin and other serum proteins by sulfisoxazole in neonates is well documented. However, because drug bound to plasma proteins cannot be eliminated by the kidney, an increase in free drug concentration also may increase its clearance.

The amount of body fat is substantially lower in neonates than in adults, which may affect drug therapy. Certain highly lipid-soluble drugs are distributed less widely in infants than in adults. The apparent volume of distribution of diazepam has ranged from 1.4 to 1.8 L/kg in neonates and from 2.2 to 2.6 L/kg in adults. In recent years, the number of mothers breastfeeding their infants has climbed. Thus, certain drugs distributed in breast milk may pose problems for the infants. The American Academy of Pediatrics (AAP) recommends that bromocriptine, cyclophosphamide, cyclosporine, doxorubicin, ergotamine, lithium, methotrexate, phenidone, codeine and all drugs of abuse (e.g., amphetamine, cocaine, heroin, marijuana, and phencyclidine [PCP]) not be used during breastfeeding. Use of nuclear medicines should be stopped temporarily during breastfeeding. Note that these recommendations are based on limited data; other drugs taken over a prolonged period by the mother also may be toxic to the infant. For example, acenbutolol, aspirin, atenolol, clemastine, phenobarbital, primidone, sulphasalazine, and 5-aminosalicylic acid have been associated with adverse effects in some nursing infants. Unless the benefits outweigh the risks, the mother should avoid using any drug during pregnancy and while breastfeeding.

### METABOLISM

Drug metabolism is substantially slower in infants than in older children and adults. There are important differences in the maturation of various pathways of metabolism within a premature infant. For example, the sulfation pathway is well developed, but the glucuronidation pathway is undeveloped in infants. Although acetaminophen metabolism by glucuronidation is impaired in infants compared with adults, it is partly compensated for by the sulfation pathway. The cause of the tragic chloramphenicol-induced gray baby syndrome in newborn infants is decreased metabolism of chloramphenicol by glucuronyltransferases to the inactive glucuronide metabolite. This metabolic pathway appears to be age related and may take several months to 1 year to develop fully, as evidenced by the increase in clearance with age up to 1 year.

Interestingly, higher serum concentrations of morphine are required to achieve efficacy in premature infants than in adults, in part because infants are not able to metabolize morphine adequately to its 6-glucuronide metabolite (20 times more active than morphine). This is balanced to some degree by the fact that the clearance of morphine quadruples between 27 and 40 weeks of post-conceputal age.

Metabolism of drugs such as theophylline, phenobarbital, and phenytoin by oxidation also is impaired in newborn infants. However, the rate of metabolism is more rapid with phenobarbital and phenytoin than with theophylline, perhaps because of the involvement of different cytochrome P450 (CYP) isozymes. Total clearance of phenytoin by CYP2C9 and, to a lesser extent, by CYP2C19 surpasses adult values by 2 weeks of age, whereas theophylline clearance is not fully developed for several months. Two additional observations about theophylline metabolism by CYP1A2 in pediatric patients should be noted. First, in premature infants receiving theophylline for treatment of apnea, a significant amount of its active metabolite caffeine may be present, unlike the case in older children and adults. Second, theophylline clearance in children 1 to 9 years of age exceeds the values in infants as well as adults. Thus, a child with asthma often requires markedly higher doses on a weight basis of theophylline compared with an adult. Because of decreased metabolism, doses of drugs such as theophylline, phenobarbital, phenytoin, and diazepam should be decreased in premature infants.

The clearance of unbound S-warfarin, a substrate of CYP2C9, was substantially greater in prepubertal children than among pubertal children and adults even after adjustment for total body weight. Finally, clearance of caffeine, metabolized by demethylation, declines to adult values when girls reach Tanner stage II (early puberty) and boys reach Tanner stages IV and V (late puberty). The knowledge of pharmacogenetics and pharmacogenomics now is being applied to patient care in some instances. 6-Mercaptopurine (6-MP), a drug commonly used in pediatric leukemias, undergoes catabolism that is facilitated by thiopurine S-methyltransferase (TPMT). The inherited deficiency (an autosomal recessive trait), which occurs in 6% to 11% of patients, is primarily explained by three polymorphisms in the TPMT gene (*2, *3A, and *3C). Children homozygous for one of the variant alleles require 6-MP dose reduction of approximately 90%, and heterozygotic children need a dose reduction of approximately 50% to achieve survival rates observed in patients receiving full doses in the absence of TPMT deficiency. Thus, TPMT screening is recommended to identify patients with genotypes associated with TPMT deficiency who may benefit from dose reductions to prevent toxicity.

### ELIMINATION

Drugs and their metabolites are often eliminated by the kidney. The glomerular filtration rate (GFR) may be as low as 0.6 to 0.8 mL/min per 1.73 m² (0.006 to 0.008 mL/s/m²) in preterm infants and approximately 2 to 4 mL/min per 1.73 m² (0.02 to 0.04 mL/s/m²) in term infants. The processes of glomerular filtration, tubular secretion, and tubular reabsorption determine the efficiency of renal excretion. These processes may not develop fully for several weeks to 1 year after birth.

Studies in infants have shown that tobramycin clearance during the first postnatal week may increase with an increase in gestational age. In infants up to 1 month after birth, postnatal age also was correlated directly with aminoglycoside clearance. Thus, premature infants require a lower daily dose of drugs eliminated by the kidney during the first week of life; the dosage requirement then increases with age.

Because of immature renal elimination, chloramphenicol succinate cannot accumulate in premature infants. Although chloramphenicol succinate is inactive, this accumulation may be the reason for an increased bioavailability of chloramphenicol in premature infants compared with older children. These data indicate that dose-related toxicity may result from an underdeveloped glucuronidation pathway as well as increased bioavailability of chloramphenicol in premature infants.

### DRUG EFFICACY AND TOXICITY

Besides the pharmacokinetic differences previously identified between pediatric and older patients, factors related to drug efficacy and toxicity also should be considered in planning pediatric pharmacotherapy. Unique pathophysiologic changes occur in pediatric patients with some disease states.
Examples of pathophysiologic and pharmacodynamic differences are numerous. Clinical presentation of chronic asthma differs in children and adults. Children present almost exclusively with a reversible extrinsic type of asthma, whereas adults have nonspecific, nonatopic bronchial irritability. This explains the value of adjunctive hyposensitization therapy in the management of pediatric patients with extrinsic asthma.

The maintenance dose of digoxin is substantially higher in infants than in adults. This is explained by a lower binding affinity of receptors in the myocardium for digoxin and increased digoxin-binding sites on neonatal erythrocytes compared with adult erythrocytes. Insulin requirements are highest during adolescence because of the individual’s rapid growth. Growth hormone therapy has allowed children with growth hormone deficiency to attain greater adult height. However, a study has shown that in “normal” short children (without growth hormone deficiency), early and rapid pubertal progression by growth hormone therapy may lead to a shorter final adult height than may have been attained naturally. This finding emphasizes the need for identifying specific indications for the effective and safe use of drugs in pediatric patients.

Certain adverse effects of drugs are most commonly seen in the newborn period, whereas other toxic effects may not be apparent for a long period of time because of difficulty in assessing extended medication safety. Promethazine now is contraindicated for use in children younger than 2 years because of the risk of severe respiratory depression. Chloramphenicol toxicity is increased in newborns because of immature metabolism and enhanced bioavailability. Similarly, propylene glycol, which is added to many injectable drugs, including phenytoin, phenobarbital, digoxin, lorazepam, vitamin D, and hyalurazline, to increase their stability, can cause hyperosmolality in infants. It is also present in formulations of oral drugs, including acetaminophen, dipherhydramine, furosemide, ibuprofen, and prednisone.

Benzyl alcohol was a popular preservative used in intravascular flush solutions until a syndrome of metabolic acidosis, seizures, neurologic deterioration, gasping respirations, hepatic and renal abnormalities, cardiovascular collapse, and death was described in premature infants. A decline in both mortality and the incidence of major intraventricular hemorrhage was documented after use of benzyl alcohol was stopped in low-birth-weight infants. However, a study has shown that in “normal” short children (without growth hormone deficiency), early and rapid pubertal progression by growth hormone therapy may lead to a shorter final adult height than may have been attained naturally. This finding emphasizes the need for identifying specific indications for the effective and safe use of drugs in pediatric patients.

Some drugs may be less toxic in pediatric patients than in adults. Aminoglycosides appear to be less toxic in infants than in adults. In adults, aminoglycoside toxicity is related to both peripheral compartment accumulation and the individual’s inherent sensitivity to these tissue concentrations. Although neonatal peripheral tissue compartments for gentamicin have been reported to closely resemble those of adults with similar renal function, gentamicin infrequently is nephrotoxic in infants. This dissimilarity in the incidence of nephrotoxicity implies that newborn infants have less inherent tissue sensitivity for toxicity than do adults.

The differences in efficacy, toxicity, and protein binding of drugs in pediatric versus adult patients raise an important question about the acceptable therapeutic range in children. Therapeutic ranges for drugs are first established in adults and often are applied directly to pediatric patients, but specific efficacy and safety studies should be conducted in pediatric patients to define optimal therapeutic ranges of drugs.
Are antidepressants safe and effective in children and adolescents? Because of observations of increased suicidality among adolescents (and adults, for that matter), experts are questioning whether these medications merely bring out an increased suicide risk that the patient has suppressed or has been too depressed to act on, or these medications actually increase the risk per se through some pharmacologic effect. Some selective serotonin reuptake inhibitors (SSRIs) — fluoxetine, sertraline, and fluvoxamine — are approved for use in pediatric patients in the United States. The British regulatory agency banned the use of another SSRI, paroxetine, in 2003 after analysis of the data indicated the occurrence of suicidal thoughts or episodes of self-harm at a rate 1.5 to 3.2 times higher than that with placebo. Subsequently, the FDA added a black box warning about the use of and need for monitoring SSRI therapy in pediatric patients, and FDA action has continued in this arena; thus, these drugs should be used cautiously with consideration of risks versus benefits.

### FACTORS AFFECTING PEDIATRIC THERAPY

5 Because most drugs are either metabolized by the liver or eliminated by the kidneys, hepatic and renal diseases are expected to decrease the dosage requirements in patients. Nevertheless, not all diseases require lower doses of drugs. For instance, patients with cystic fibrosis require larger doses of certain drugs to achieve therapeutically effective concentrations.42

### Hepatic Disease

Because the liver is the main organ for drug metabolism, drug clearance usually is decreased in patients with hepatic disease. However, most studies on the influence of hepatic disease on dosage requirements have been performed in adults, and these data may not be extrapolated uniformly to pediatric patients.

Drug metabolism by the liver depends on complex interactions among hepatic blood flow, ability of the liver to extract the drug from the blood, drug binding in the blood, and both type and severity of hepatic disease. Routine hepatic function tests, such as determinations of serum aspartate aminotransferase, serum alanine aminotransferase, alkaline phosphatase, and bilirubin levels, have not correlated consistently with drug pharmacokinetics. Furthermore, because of different pathologic changes in various types of hepatic diseases, patients with acute viral hepatitis may have different abilities to metabolize drugs than patients with alcoholic cirrhosis.43

On the basis of hepatic extraction characteristics, drugs can be divided into two categories. The first category consists of drugs with a high hepatic extraction ratio (>0.7; such drugs include morphine, meperidine, lidocaine, and propranolol). Clearance of these drugs is affected by hepatic blood flow. Decreased hepatic blood flow in the presence of disease states such as cirrhosis and congestive heart failure is expected to decrease the clearance of drugs with high extraction ratios. The second category consists of drugs with a low extraction ratio (<0.2) and a low affinity for plasma proteins. Metabolism of these drugs (e.g., theophylline, chloramphenicol, and acetyaminophen) is influenced mainly by hepatocellular function and not as much by changes in hepatic blood flow or plasma protein binding. One report suggested that theophylline clearance may decrease by 45% in a child with acute viral hepatitis.43 Because of a lack of specific data on dosage adjustment in hepatic disease, drug therapy should be monitored closely in pediatric patients to avoid potential toxicity from excessive doses, particularly for drugs with narrow therapeutic indices.

### Renal Disease

Renal failure decreases the dosage requirement of drugs eliminated by the kidneys. Again, because of limited studies, dosage adjustments in pediatric patients are based largely on data obtained in adults. For many important drugs, such as aminoglycoside antibiotics, renal clearance or rate of elimination is directly proportional to the GFR, as measured by endogenous renal creatinine clearance.

In clinical practice, GFR can be estimated from prediction equations such as the Schwartz formula, which takes into account serum creatinine concentration and the patient’s height, gender, and age. The advantage of estimating GFR using the Schwartz equation is rapid determination and the avoidance of a cumbersome 24-hour urine collection.44 The following formula is used to estimate GFR:

$$GFR = K \times L/S_c$$

where GFR is expressed in milliliters per minute per 1.73 m² of BSA, $K$ = age-specific constant of proportionality (see below), $L$ = child’s length in centimeters, and $S_c$ = serum creatinine concentration in milligrams per deciliter. Alternatively, for serum creatinine concentration expressed in μmol/L, the equation becomes:

$$GFR = K \times L \times 88.4/S_c$$

Conversion of GFR to units of mL/min/m² requires multiplication of GFR expressed in milliliters per minute per 1.73 m² by 0.00963.

<table>
<thead>
<tr>
<th>Age</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year of age</td>
<td>0.33</td>
</tr>
<tr>
<td>low-birth-weight infant</td>
<td>0.45</td>
</tr>
<tr>
<td>2- to 12-year-old child</td>
<td>0.55</td>
</tr>
<tr>
<td>13- to 21-year-old female</td>
<td>0.55</td>
</tr>
<tr>
<td>13- to 21-year-old male</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Studies comparing the Schwartz-predicted GFR versus measured GFR noted that the Schwartz formula overestimated GFR in patients with decreasing GFR. The formula may not provide an accurate estimation of GFR in patients with rapidly changing serum creatinine concentrations, as seen in the critical care setting; in infants younger than 1 week; and in patients with obesity, malnutrition, or muscle wasting. Factors that interfere with serum creatinine measurement also may cause errors in estimation of GFR.

Changes in laboratory methods for measuring serum creatinine levels have led to the development of an updated equation to estimate GFR in children with mild to moderate renal function impairment. Use of the old Schwartz equation with a serum creatinine level determined using current laboratory methods leads to an overestimation of GFR by approximately 10% to 20%.56 Schwartz et al. assessed GFR in 349 children enrolled in the Chronic Kidney Disease in Children Study, ages 1 to 16 years, using plasma iohexol clearance.57 The updated formula derived from changes in laboratory methods for serum creatinine measurement is as follows:

$$eGFR(\text{mL/min}/1.73m^2) = 39.1 \times [\text{height(m)}/S_c(mg/dL)]^{0.516} \times [1.8/cystatin C(mg/L)]^{0.284} \times [30/BUN(mg/dL)]^{0.169} \times [1.099]^{0.186} \times [\text{weight(m)/1.4}]^{0.186}$$

A simplified prediction equation was also proposed:

$$eGFR(\text{mL/min}/1.73m^2) = 0.413 \times [\text{height(cm)}/S_c]$$

Note: The updated formulas do not provide an accurate estimation of GFR in patients with normal renal function or patients with
advanced renal failure because these populations are outside the range of those enrolled in the Chronic Kidney Disease in Children Study. (To use these equations, $S_C$ expressed in μmol/L must first be divided by 88.4 to obtain conventional units of mg/dL, and blood urea nitrogen expressed in mmol/L must be divided by 0.357 to obtain conventional units of mg/dL. Conversion of GFR to units of mLs/min/m² requires multiplication of GFR expressed in milliliters per minute per 1.73 m² by 0.00963.)

Serum drug concentrations should be monitored for drugs with narrow therapeutic indices and eliminated largely by the kidneys (e.g., aminoglycosides and vancomycin) to optimize therapy in pediatric patients with renal dysfunction. For drugs with wide therapeutic ranges (e.g., penicillins and cephalosporins), dosage adjustment may be necessary only in patients with moderate to severe renal failure.

### Cystic Fibrosis

Drug therapy in pediatric patients with cystic fibrosis has been reviewed. For unknown reasons, these patients require increased doses of certain drugs. Studies have reported higher clearance of drugs such as gentamicin, tobramycin, netilmicin, amikacin, dicyclaxacin, claxacillin, azlocillin, piperacillin, and theophylline in patients with cystic fibrosis compared with patients without the disease. The apparent volume of distribution of certain drugs also may be altered in cystic fibrosis. The severity of the illness may influence the change in dosage requirements, but this is not certain. Chapter 18 reviews these changes in detail.

### Obesity

One-third of American children and adolescents are obese or overweight. The prevalence of pediatric obesity has nearly tripled for children 2 to 5 years of age and for those 12 to 19 years of age; it has quadrupled for children 6 to 11 years of age over the past 30 years. Children and adolescents are classified as being overweight or obese according to CDC age- and gender-specific percentiles for body mass index (BMI). The CDC and the AAP categorize overweight children as having a BMI percentile greater than 85th to less than 95th and obese children as having a BMI percentile of greater than the 95th percentile. Obese children are at risk for metabolic complications and the development of comorbid conditions, including high blood pressure, high cholesterol, type 2 diabetes mellitus, nonalcoholic fatty liver disease, polycystic ovary disorder, cholecystitis, gastroesophageal reflux disease, and obstructive sleep apnea. During a 1999 to 2008 study period, 49% of overweight and 61% of obese adolescents had one or more cardiovascular risk factor, which included prehypertension or hypertension, low high-density lipoprotein cholesterol, and elevated fasting glucose level.

A 50% increased recurrence of acute lymphoblastic leukemia in obese children older than 10 years of age compared with lean children with cancer has also been reported. Studies show that obesity can directly impair the antileukemia efficacy of first-line chemotherapeutic agents and accelerate leukemia progression. In addition, higher rates of life-threatening or fatal complications to chemotherapy have been reported with obese children and adolescents than normal-weight children. A retrospective study compared safety and efficacy between obese and normal-weight children who received methotrexate, teniposide, etoposide, and cytarabine for treatment of acute lymphoblastic leukemia. No significant difference existed on the basis of BMI in the rate of complete remission, overall survival, incidence of relapse, and frequency of toxicity. Chemotherapy doses were based on BSA calculated using total body weight for all children. Findings suggest that the doses of cytarabine, etoposide, teniposide, and methotrexate in obese children should be based on BSA calculated using total body weight. These findings are consistent with the recommendations for appropriate chemotherapy dosing in adult obese patients, which advise use of the patient’s actual body weight when calculating the dose and not limiting the dose or using an adjusted ideal body weight unless there is an established dosing limit. Limiting the dose in obese patients may lead to poorer outcomes and undertreatment.

Obese children have a higher proportion of body fat, which generally results in a higher volume of distribution ($V_D$) for lipophilic drugs and a lower $V_D$ for hydrophilic medications compared with normal-weight children. Obese children have higher total body water, lower percent lean mass, increased organ mass, and greater cardiac output, GFR, and serum creatinine concentrations than normal-weight children. Many antibiotics are hydrophilic medications that distribute to extracellular water. Adipose tissue contains approximately 30% water, meaning that many antibiotics will not distribute adequately in obese patients.

Correction factors have been used to adjust drug dosing in obese children. A correction factor is multiplied by the actual body weight less the ideal body weight, and this figure is added to the ideal body weight. The drug dose is then determined based on this weight. Correction factors are 0.3 for $β$-lactams, 0.45 for ciprofloxacin, and 0.4 for aminoglycosides.

When possible, plasma drug level monitoring should be used to adjust dosing; very few studies have been conducted to establish effective drug dosing information for obese children.

Vancomycin distributes into total body water and other tissues and is eliminated primarily by glomerular filtration. Vancomycin is empirically dosed using actual body weight in overweight and obese children; the dose is not capped at the usual maximum adult dose. Every-8-hour dosing is used initially; the frequency can be increased to every-6-hour dosing for complicated infections using serum concentration monitoring to individualize the dose.

Pharmacokinetic studies of anesthetic agents in obese children have not been conducted to characterize distribution, adipose tissue accumulation, and elimination. One study showed that obese children lose consciousness at a significantly lower propofol dose than patients with a healthy weight. Whereas an IV propofol dose of 2 mg/kg was effective in 95% of children with BMIs above the 95th percentile, those with lower BMIs each required a higher dose of 3.2 mg/kg.

Specific studies are needed to identify the effects of childhood obesity on pharmacokinetics, pharmacodynamics, and efficacy of medications so that optimal drug dosing can be determined for this population.

### Other Conditions

Although specific dosage guidelines are not available, pediatric patients with gastrointestinal disease (e.g., celiac disease, gastroenteritis, and severe malabsorption) may require dosage adjustments. Hypoxemia also has been shown to decrease the elimination of amikacin in low-birth-weight infants. Critically ill adult and pediatric patients with severe head trauma require higher than normal doses of phenytoin in part because of increased intrinsic clearance.

### ISSUES IN PEDIATRIC DRUG THERAPY

#### Pain Management

For many years, the term pain could not be found in the index of any major pediatric medicine or pediatric surgical textbook. The prevailing wisdom was that neonates did not experience pain...
because of their inadequately developed neuroendocrine systems and nerve pathways. During the last years of the 20th century, however, many research and clinical studies were performed in the areas of pain management and assessment of neonates, infants, children, and adolescents. Today, results of these discoveries have been incorporated into clinical practice, making effective pain therapy a standard of care and pain assessment the fifth vital sign in modern pediatric practice.67

The basic mechanisms of pain perception in infants and children are similar to those of adults, except that pain impulse transmission in neonates occurs primarily along slow-conducting, nonmyelinated C fibers rather than along myelinated Aβ fibers. In addition, pain signal transmission in the spinal cord is less precise, and descending inhibitory neurotransmitters are lacking. As a result, neonates and young infants may perceive pain more intensely and be more sensitive to pain than older children or adults.68 It is now known that previous pain experience leads to long-term consequences such as alterations in response to a subsequent painful event.69 Taddio et al.70,71 reported that boys circumcised with the topical anesthetic eutectic mixture of local anesthetics (EMLA) had lower pain responses to subsequent immunizations than those who were circumcised without topical anesthesia. An inadequately treated initial painful procedure may decrease the effect of adequate analgesia in subsequent procedures as a result of altered pain response patterns.

Children consistently report that needles and shots are what they fear most. However, with the current immunization schedule that recommends 14 to 33 injections before adolescence, interventions to decrease injection pain need to be performed (eTable 7-1).72–77

Pharmacologic pain management for medical conditions and surgical and postoperative events has progressed considerably over the past decade with the use of continuous opioid infusions, epidural anesthesia, peripheral nerve blockade, local anesthetics, nonsteroidal antiinflammatory drugs, different routes for traditional agents (i.e., transmucosal and transdermal), and nonopioid adjuvant drugs (eTable 7-2).78–82 New pain management techniques, education, research, and increasing awareness of pain management options have helped to improve the quality of life in children.

### Drug Administration

Drugs often are given by the IV route to seriously ill patients. Syringe pumps are widely used for administration of IV drugs. Important steps in successfully administering IV drugs include selecting the drug, calculating the dose, preparing the infusion, programming the infusion pump, and delivering the infusion. Use of “smart” pumps is preferred because they can recognize syringes and have drug libraries and dose limits as safety features. The pumps should be accurate, precise, and easy to use; accept syringes and administration sets from various manufacturers; offer extensive delivery mode combinations, including milliliters per hour, body weight, mass, volume over time, custom dilution and intermittent, loading dose, bolus dose, standby, and volume limit; have wide-ranging flow rates and rate to keep vein open; and have an adequate internal battery capacity.

No single infusion system is ideal for delivery of all drugs in all institutions for all patients. Each facility must be cognizant of problems of drug delivery and develop specific guidelines for IV infusions. At each institution, specific guidelines should be provided for administration of each drug. These guidelines take into account various infusion rates and provide consistency of delivery with each dose. As long as the time for actual delivery is known, times to obtain blood samples for measurement of drug concentration can be adjusted accordingly to generate meaningful data.

#### eTable 7-1 Techniques for Minimizing Pain Caused by Injection

<table>
<thead>
<tr>
<th>Pharmacologic Methods</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMLA</strong>72</td>
<td><strong>Advantages:</strong> Penetrates the skin to provide anesthesia to a depth of 5 mm; effective in decreasing the pain of IM and subcutaneous injections, venipuncture, IV cannulation, lumbar puncture, circumcision, skin-graft harvesting, and laser dermal therapy; safe and effective in newborns &gt; 37 weeks’ gestation. <strong>Disadvantages:</strong> Requires 1 hour before onset of adequate anesthesia, has a vasoconstrictive effect that may make starting IV catheters difficult, may induce methemoglobinemia.</td>
</tr>
<tr>
<td><strong>J-tip with buffered lidocaine</strong>72,76</td>
<td><strong>Advantages:</strong> Provides dermal anesthesia to a depth of 5–8 mm within 1–3 min; effective in decreasing the pain of IV cannulation. <strong>Disadvantage:</strong> Makes a popping noise; this can scare a patient who is not properly prepared.</td>
</tr>
<tr>
<td><strong>Vapocoolant sprays</strong> (ethyl chloride or dichlorodifluoromethane)74</td>
<td><strong>Advantages:</strong> Vapocoolant is sprayed directly onto the skin or applied to a cotton ball that is held on the area to be anesthetized; provides local anesthesia within 15 seconds; effective in reducing injection pain in children 4–6 years of age. <strong>Disadvantages:</strong> Brief duration of action, so procedure should be completed in 1 or 2 min; may not be effective in reducing injection pain in infants age 2–6 months.</td>
</tr>
<tr>
<td>**Local anesthetic (lidocaine)**75</td>
<td><strong>Advantage:</strong> Reduces the pain of subsequent needle insertion. <strong>Disadvantage:</strong> Local anesthetic injection itself is associated with pain and burning sensation.</td>
</tr>
<tr>
<td><strong>Pacifier with sucrose</strong>76</td>
<td><strong>For preterm neonates:</strong> 0.1–0.4 mL of a 12%–24% sucrose solution (place on pacifier or the tongue 2 min before procedure); <strong>for term neonates:</strong> 1–2 mL of a 12%–24% sucrose solution (place on pacifier or the tongue 2 min before procedure). <strong>Advantage:</strong> Noninvasive method to reduce pain associated with needle insertion in infants. <strong>Disadvantage:</strong> Sucrose solution’s effect in reducing pain gradually decreases over time.</td>
</tr>
</tbody>
</table>

**Other Techniques**

<table>
<thead>
<tr>
<th>Characteristics</th>
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<tbody>
<tr>
<td><strong>Site selection</strong>77</td>
</tr>
<tr>
<td><strong>Z-tract technique</strong></td>
</tr>
<tr>
<td><strong>Behavioral</strong></td>
</tr>
</tbody>
</table>

EMLA, eutectic mixture of lidocaine and prilocaine; IM, intramuscular.
Alteration of Dosage Forms

Many drugs used in pediatric patients are not available in suitable dosage forms. This necessitates dilution of high concentrations of drugs intended for adult patients. Examples of these drugs include atropine, carbamazepine, diazepam, digoxin, epinephrine, hydralazine, insulin, morphine, phenobarbital, and phenytoin. Volumes ranging from 0.01 to 0.1 mL must be measured to dispense these drugs for use in infants. This obviously can be associated with large errors in measurements, and such errors have caused intoxication and death in infants.36 Further addition of this vehicle may not be wise. It is much easier to administer a drug in a suitable preparation than it is to attempt to dilute a drug into a solution of a diluent that is not intended for use with this drug. Some diluents, such as propylene glycol, are not intended for pediatric use, and it is assumed that their compatibility is not known.38

IV or PO bolus administration (not as needed) Weak opioids (e.g., codeine, hydrocodone, oxycodone) often are combined with acetaminophen or an NSAID for moderate pain. With dose escalation of combination oral products, be aware that the dose does not exceed recommended daily amounts for acetaminophen or ibuprofen. 1%–7% of the general population and up to 28% of some ethnic groups have a genetic variation in the enzyme cytochrome P450 2D6 that causes codeine to be converted to morphine faster and more completely. In 2012, the FDA issued a Drug Safety Communication stating that codeine use in certain children after tonsillectomy or adenoidectomy for obstructive sleep apnea syndrome has led to deaths and life-threatening respiratory depression. Consider alternative analgesics for children undergoing tonsillectomy or adenoidectomy. If codeine or codeine-containing products are prescribed, use the lowest effective dose for the shortest period of time on an as-needed basis. IV administration of codeine has been associated with allergic reactions related to histamine release. Parenteral administration of codeine is not recommended. Intermittent opioid administration is associated with wide fluctuation between peak and trough levels, so the patient may alternate between peak blood levels associated with untoward effects and trough levels associated with inadequate pain relief when being treated for severe pain.

Oxycodone and morphine are available in a sustained-release formulation for use with chronic pain (not acute pain). The tablet must be swallowed whole and cannot be administered to patients through gastric tubes.

A number of extemporaneous formulations for oral, IV, and rectal administration are included in a compilation of products for use in pediatric patients.36 However, a specific reference on the stability of many drug formulations is lacking and emphasizes the need for continued research in this area.

Drug administration into the middle ear, nose, or eye of a child requires special attention. Certain drugs (e.g., sodium valproate and phenytoin) can be administered rectally to infants who have limited access for IV drug administration or if oral drug administration cannot be accomplished.

Transdermal drug delivery can be used in pediatric patients to avoid problems of drug absorption from the oral route and complications from the IV route and to maximize duration of effect and minimize adverse effects of drugs. As discussed earlier in this chapter, methylphenidate (Daytrana) now is available as a transdermal patch for children with ADHD. Unfortunately, the commercially available transdermal dosage forms (e.g., clonidine and scopolamine) are not intended for pediatric patients; these would deliver doses much higher than needed for infants and children.

Medication Adherence

The issue of medication adherence is more complex in pediatric patients than in adults. Caregivers of young patients must appreciate the importance of understanding and following the prescribing information. In one study, medication adherence was considered to be a problem in nearly 60% of adolescents (age 12–15 years) with asthma. Approximately 40% of patients had severe denial regarding their asthma and its severity. Nearly 80% of patients had preventable asthma exacerbations.37 Among the factors that can negatively affect adherence are poor communication between the physician and patient or parent,
insufficient prescribing information, lack of understanding about the severity of illness by the patient or parent, lack of interest (e.g., among adolescents), fear of side effects, failure of the patient or parent to remember to administer the drugs, inconvenient dosage forms or dosing schedules involving administration of three or more doses daily, and unpalatability of drug products. Studies in pediatric volunteers have compared the palatability of antibiotics, and the data may have important implications for adherence in children.

Dose Requirements
Medication doses often are based on the body weight of neonates, infants, and children (e.g., milligrams per kilogram of body weight per day to be given in one or more portions daily). However, certain drugs, including antineoplastic agents, may be given based on BSA (e.g., milligrams per square meter in one or more doses daily). In either case, the total amount of weight- or surface area–based individual or daily dose in a pediatric patient, especially an adolescent, should not exceed the amount of drug indicated in an adult patient.

An additional challenge in managing pediatric drug therapy is understanding the effects of obesity on a population that relies on weight-based dosing. As mentioned earlier, the number of children who are overweight or obese has increased markedly over the past 4 decades. Using ideal body weight versus total body weight to calculate a weight-based dose or to determine BSA can result in a large variance in obese patients. Additional pharmacokinetic studies are needed to study the effects of obesity on drug distribution, protein binding, and clearance and to identify whether dosing should be adjusted according to total body weight or ideal body weight to achieve consistent drug exposure for individual drugs. Generally, the highest drug dose recommended for a child is the maximum dose approved for adults. However, determining the highest dose of certain drugs for use in children without a known maximum dose for adults (e.g., IV immunoglobulin, infliximab, rituximab, and liposomal amphotericin B [AmBisome]) can be difficult.

Drug Interactions
Drug interaction studies in pediatric age groups generally are lacking. The data often are extrapolated from studies in adult populations. Special attention should be given to adolescents, who may concurrently use alcohol, recreational or illicit drugs, or other prescription or nonprescription medications without the knowledge of the primary healthcare provider, who must attempt to determine their use to avoid drug interactions.

Complementary and Alternative Therapy
In a study of patients between 3 weeks and 18 years (mean, 5.3 years) of age, 45% of caregivers were giving a product to the children; 27% had given three or more products in the past year. The most commonly used products were aloe plant or juice (44% of those reporting use of herbal therapies), Echinacea (33%), and sweet oil (25%). The most dangerous combination was ephedra (which was withdrawn from the U.S. market in 2004) with albuterol given to adolescents with asthma. Most caregivers did not recognize potential adverse effects or drug interactions associated with herbs. Friends or relatives were the main sources of information for 80% of caregivers.

Little is known about the efficacy of herbal products in infants, children, and adolescents. Healthcare professionals must ask caregivers specifically about the use of complementary and alternative treatments to minimize the adverse effects and costs associated with ineffective therapies.

Medication Safety
The Institute of Medicine reported that between 44,000 and 98,000 Americans each year die as a result of medical errors in hospitals. According to this report, the vast majority of medical errors that cause harm to patients are preventable. Healthcare professionals have a responsibility for creating a safe medication environment and reducing risk to a vulnerable pediatric population.

Pediatric medication errors commonly occur at the medication-ordering step because of the multiple calculations required for weight-based dosing and the adjustments needed for providing therapy to the developing pediatric patient. The United States Pharmacopeia (USP) Center for the Advancement of Patient Safety states that risk to patients when performing repeated calculations involving multiple steps can be minimized using computer-based algorithms. Because the medication-preparation step is also a high-hazard point owing to the need for dilution or manipulation of commercially available products only available in adult doses, the USP recommends that compounded pediatric medications be prepared and labeled in the pharmacy and verified by a pharmacist. In 2006 and 2007, there were several reports of heparin-dispensing errors to neonatal patients caused by different concentrations of the same medication used to service the needs of neonates and adults (neonatal and adult product mix-up). In 2008, The Joint Commission issued an alert on preventing errors related to commonly used anticoagulants. Among drug administration–related errors, wrong dose, wrong technique, and wrong drug are the three most common errors and may be related to an inability to access pediatric drug information. In 2001, the Agency for Healthcare Research and Quality published an evidence-based assessment of patient safety practices that prevent or reduce medication errors. Risk-reduction strategies include placing a clinical pharmacist on pediatric wards in hospitals, simplifying the medication-use system, ordering standardized concentrations and doses, implementing computerized physician order-entry systems with dose range checking, dispensing pharmacy-prepared or ready-to-administer doses, standardizing infusion equipment, using smart infusion pumps, using bar-coded medications and bar-coding systems that check the medication at the point of care, and implementing computerized adverse event detection systems. Identifying and understanding the high-hazard areas or points of failure in the medication-use process will help in designing strategies that prevent problems before they arise.

CONCLUSIONS
Although tremendous progress has been made in the area of pediatric pharmacotherapy, many questions remain unanswered. The pharmacokinetics of many important drugs have been elucidated, but their pharmacodynamics have not been explored fully. Similarly, the effect of disease states and patient characteristics, such as genetic status, have not been studied for most drugs. The effect of these factors on the development of CYP isozymes (e.g., CYP3A4, CYP2D6, CYP1A2, CYP2C9, and CYP2C19), other enzymes, and P-glycoprotein needs to be studied (see eChaps. 5 and 6). Similarly, comparative efficacy and safety data for many therapies are unavailable. Studies on the influence of drug therapy on clinical and economic outcomes and on quality of life in pediatric patients are needed.

The development of new drugs has contributed to improved patient care. FDA regulations (Best Pharmaceuticals for Children Act and Pediatric Research Equity Act) can require the industry to conduct studies and seek labeling of important drugs for use in pediatric patients. As an incentive, a 6-month patent extension and waiver of supplemental new drug application fee are offered to the industry. This should encourage the industry to develop and market more drugs for the pediatric population. However, greater
emphasize also should be placed on disease prevention. Millions of children die because of preventable diseases, particularly in
developing countries of the world. Administration of vaccines
and control of diarrhea alone could save millions of these lives
annually. However, many countries may lack resources for vac-
cinations. The infant mortality rate in the United States is nearly
twice as high among blacks as whites. Improved prenatal care;
educational programs; and avoidance of alcohol, smoking, and
drugs of abuse during pregnancy may decrease mortality rates as
well as morbidity from illnesses, including acquired immunodefi-
ciency syndrome.

Finally, efforts should be made to offer evidence-based phar-
macotherapy. This often is difficult in pediatric populations when
the drugs must be used outside the guidelines and indications approved
by the FDA. Institutions should develop guidelines for the use of
drugs in specific diseases and for the use of high-cost drugs such as
colony-stimulating factors, monoclonal antibodies, dornase alfa,
epoetin alfa, immunoglobulins, surfactants, and growth hormones.

Although much needs to be learned about the optimization of
therapy, it is encouraging to witness the continued growth of knowl-
edge in this area that has improved the quality of life and survival
from pharmacotherapy in pediatric patients.

ABBREVIATIONS

ADHD  attention-deficit/hyperactivity disorder
AAP   American Academy of Pediatrics
BMI   body mass index
BSA   body surface area
CDC   Centers for Disease Control and Prevention
CYP   cytochrome P450
EMLA  eutectic mixture of local anesthetics
FDA   Food and Drug Administration
GFR   glomerular filtration rate
OTC   over the counter
PCA   patient-controlled analgesia
SSRI  selective serotonin reuptake inhibitor
USP   United States Pharmacopeia

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