Chapter e20: Pediatrics: General Topics in Pediatric Pharmacotherapy

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 1, Pediatric Pharmacotherapy, Nutrition, and Neonatal Critical Care.

KEY CONCEPTS

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1. 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.
2. 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.
3. 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.
4. The effectiveness and safety of drugs may vary among age groups and from one drug to another in pediatric versus adult patients.
5. Concomitant diseases may influence dosage requirements to achieve a targeted effect for a specific disease in children.
6. Use of weight-based dosing of medications for obese children may result in suboptimal drug therapy.
7. The myth that neonates and young infants do not experience pain has led to inadequate pain management in this pediatric population.
8. Special methods of drug administration are needed for infants and young children.
9. 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.
10. The pediatric medication-use process is complex and error prone because of the multiple steps required in calculating, verifying, preparing, and administering doses.

BEYOND THE BOOK

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Visit the US Food and Drug Administration Website and navigate to the New Pediatric Labeling Information Database <https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>. The Website provides comprehensive up-to-date information related to pediatric drug labeling changes. Explore available drugs, review recent labeling information for one drug of interest, and summarize the label changes. This Website is useful to enhance student understanding of available resources for pediatric drug dosing information.

INTRODUCTION

Remarkable progress has been made in the clinical management of diseases 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 may experience a variety of health problems and 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.

1 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 5.6 per 1,000 births in 2019.[1] 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, less than one-half of the drugs approved by the US Food and Drug Administration (FDA) are labeled 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 µg/mL (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 polyneuritis, 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 albumin-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 two 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 neonates, infants, and children are not available in suitable dosage forms. For example, extemporaneous liquid dosage forms of amiodarone, baclofen, captopril, hydroxyurea, tacrolimus, ursodiol, 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 neonates and 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

2 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.[2] In contrast, gastric pH remains elevated in premature infants because of immature acid secretion.[3]

In premature infants, higher serum concentrations of acid-labile drugs, such as penicillin,[4] ampicillin,[5] and nafcillin,[6] and lower serum concentrations of a weak acid such as phenobarbital[7] 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 (eg, digoxin and phenobarbital) and nutrients (eg, arabinose and xylose) have suggested that the processes of both passive and active transport may be fully developed by approximately 4 months of age.[8] Little is known about the development and expression of the efflux transporter P-glycoprotein and the intestinal drug-metabolizing enzymes and microflora, and their impact on drug absorption and bioavailability in infants and children.

Studies have shown that gastric emptying is slow in premature infants.[9] 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,[10] whereas diazepam absorption may be delayed.[11] 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 body surface area (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,[12] salicylic acid ointment, and rubbing alcohol.[13] 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.[14] The 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 (pK_a, molecular weight, and 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.[14] 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.[15] This conforms to the observed gentamicin distribution volumes of 0.48 L/kg in neonates and 0.20 L/kg in adults.[16] 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.[17]

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.[18] 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[19] and phenytoin.[20]

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.[21] However, because drug bound to plasma proteins cannot be eliminated by the kidney, an increase in free drug concentration also may increase its clearance.[22]

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 ranged from 1.4 to 1.8 L/kg in neonates and from 2.2 to 2.6 L/kg in adults.[23] 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, phenindione, codeine, and all drugs of abuse (eg, amphetamine, cocaine, heroin, marijuana, and phencyclidine) not be used during breastfeeding. Use of nuclear medicines should be stopped temporarily during breastfeeding.[24] 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, acebutolol, aspirin, atenolol, clemastine, phenobarbital, primidone, sulfasalazine, and 5-aminosalicylic acid have been associated with adverse effects in some nursing infants.[24] 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 which may develop over the weeks, months, or year(s) after birth of a premature infant.[25] For example, the sulfation pathway is well developed, but the glucuronidation pathway is undeveloped in infants.[26] 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.[27] This metabolic pathway is age related[28] and may take several months to 1 year to develop fully, as evidenced by the increase in clearance with age up to 1 year.[29]

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).[30] This is balanced to some degree

by the fact that the clearance of morphine quadruples between 27 and 40 weeks of postconceptional 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.[18] 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.[18] 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.[31] Because of decreased metabolism, daily doses of drugs such as theophylline, phenobarbital, phenytoin, and diazepam should be decreased in premature infants. CYP3A4 is the most commonly expressed enzyme for the metabolism of drugs and it may take up to one year for its full maturation.[25]

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.[32] 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).[33] 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 metabolism 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.[34]

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/1.73 m^2 (0.006-0.008 mL/s/m^2) in preterm infants and approximately 2 to 4 mL/min/1.73 m^2 (0.02-0.04 mL/s/m^2) 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 to 2 years after birth. Additional studies are needed about the ontogeny of renal transporters, for example, P-glycoprotein.[25]

Studies in infants have shown that tobramycin clearance during the first postnatal week may increase with an increase in gestational age.[17] In infants up to 1 month after birth, postnatal age also was correlated directly with aminoglycoside clearance.[29] 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 sodium succinate can accumulate in premature infants. Although chloramphenicol sodium succinate is inactive, this accumulation may be the reason for an increased bioavailability of the biologically active, chloramphenicol in premature infants compared with older children.[28] 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

4 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.[35]

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.[36] 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.[37] 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. Codeine toxicity and death have been reported after tonsillectomy and adenoidectomy in children who were ultrarapid metabolizers receiving codeine within the typical dose range.[38] Thus, codeine should not be used in these patients. Similarly, propylene glycol, which is added to many injectable drugs, including phenytoin, phenobarbital, digoxin, lorazepam, vitamin D, and hydralazine, to increase their stability, can cause hyperosmolality in infants.[39] It is also present in formulations of oral drugs, including acetaminophen, diphenhydramine, 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 solutions containing benzyl alcohol was stopped in low-birth-weight infants.[40] It is also used as a preservative in parenteral dexamethasone, methylprednisolone, enoxaparin, midazolam, and multivitamin formulations.

Ethanol is present in certain oral drugs, including phenobarbital and ranitidine, and, sorbitol is used in oral liquids, including diphenhydramine, ferrous sulfate, furosemide, ondansetron, and prednisone. The safe and acceptable levels of intake of many excipients have not been determined for infants and children.

The common cold occurs frequently in infants and children and is often treated with antihistamines, decongestants, antitussives, and expectorants. Given the lack of evidence for their efficacy and serious toxicities associated with overdoses, the FDA issued a public health advisory in 2008 recommending that these drugs not be used in children younger than 2 years. The manufacturers have voluntarily agreed to label these medications not for use in children younger than 4 years.

Tetracyclines are contraindicated for use in pregnant women, nursing mothers, and children younger than 8 years because these drugs can cause dental staining and defects in enamelization of deciduous and permanent teeth, as well as a decrease in bone growth.[41] However, the Centers for Disease Control and Prevention (CDC) has recommended the use of doxycycline for initial prophylaxis after suspected bioterrorism-related exposure to *Bacillus anthracis* (anthrax); the potential benefits outweigh potential risks among infants and children. Certain fluoroquinolones are indicated for infections including inhalation anthrax, complicated urinary tract infections and pyelonephritis, but their use should be restricted due to concern of adverse effects when no safe and effective alternative is available or an oral agent is used as an alternative to parenteral therapy.[42]

Some drugs may be less toxic in pediatric patients than in adults. Aminoglycosides are less toxic in infants than in adults. In adults, aminoglycoside toxicity is related to both peripheral compartment accumulation and the individual patient's inherent sensitivity to these tissue concentrations.[43] Although neonatal peripheral tissue compartments for gentamicin have been reported to closely resemble those of adults with similar kidney function,[16] 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.

FACTORS AFFECTING PEDIATRIC THERAPY

5 Because most drugs are either metabolized by the liver or eliminated by the kidneys, liver, and kidney 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 therapeutic concentrations.[44]

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 concentrations, 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.[45]

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 (greater than 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 (eg, theophylline, chloramphenicol, and acetaminophen) 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.[45] 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.

Kidney Disease

Kidney 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 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.[46,47] The following formula is used to estimate GFR:

$\mathrm{GFR} = K \times L/S_{\mathrm{Cr}}$ GFR=K×L/SCr

where GFR is expressed in milliliters per minute per 1.73 m^2 of BSA, K is the age-specific constant of proportionality (see below), L is the child's length in centimeters, and S_{Cr} is the serum creatinine concentration in milligrams per deciliter. Alternatively, for serum creatinine concentration expressed in µmol/L, the equation becomes: GFR = $K \times L \times 88.4/S_{cr}$. Conversion of GFR to units of mL/s/m^2 requires multiplication of GFR expressed in milliliters per minute per 1.73 m^2 by 0.00963.

Age	*K*
<1 year of age, low-birth-weight infant	0.33
<1 year of age, full-term infant	0.45
2- to 12-year-old child	0.55
13- to 21-year-old female	0.55
13- to 21-year-old male	0.70

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 concentrations have led to the development of an updated equation to estimate GFR in children with impaired kidney function. The use of the old Schwartz equation with a serum creatinine concentration determined using current laboratory methods leads to an overestimation of GFR by approximately 10% to 20%.[48] GFR in 349 children enrolled in the Chronic Kidney Disease in Children Study, aged 1 to 16 years, was assessed using plasma iohexol clearance.[49] The updated formula derived from changes in laboratory methods for serum creatinine measurement is as follows:

$$\mathrm{eGFR}\left(\mathrm{mL/min/1.73m^2}\right) = 39.1 \times \left(\mathrm{height}\left[\mathrm{m}\right]/S_{\mathrm{Cr}}[\mathrm{mg/dL}]\right)^{0.516} \times (1.8/\mathrm{cystatin\ C[mg/L]})^{0.294} \times (30/\mathrm{BUN[mg/dL]})^{0.169} \times (1.099)^{\mathrm{if\ male}} \times (\mathrm{height[m]}/1.4)^{0.188}$$

eGFR(mL/min/1.73m2)=39.1×(height[m]/SCr[mg/dL])0.516×(1.8/cystatin C[mg/L])0.294×(30/BUN[mg/dL])0.169×(1.099)if male×(height[m]/1.4)0.188

A simplified prediction equation (frequently referred as Bedside Schwartz equation) was also proposed:[50,51]

$$\mathrm{eGFR}\left(\mathrm{mL/min/1.73m^2}\right) = 0.413\left(\mathrm{height}\left[\mathrm{cm}\right]/S_{\mathrm{Cr}}\right)$$

eGFR(mL/min/1.73m2)=0.413(height[cm]/SCr)

The updated formulas do not provide an accurate estimation of GFR in patients with normal kidney function or patients with advanced kidney disease because these populations are outside the range of those enrolled in the Chronic Kidney Disease in Children Study. To use these equations, S_{Cr} 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 mL/s/m^2 requires multiplication of GFR expressed in mL/min/1.73 m^2 by 0.00963. In addition, the estimated GFR values may be lower than actual for infants and adolescents and higher for low birth weight infants less than 1 year.

Serum drug concentrations should be monitored for drugs with narrow therapeutic indices and eliminated largely by the kidneys (eg, aminoglycosides and vancomycin) to optimize therapy in pediatric patients with impaired kidney function. For drugs with wide therapeutic ranges (eg, penicillins and cephalosporins), dosage adjustment may be necessary only in patients with moderately to severely impaired kidney function.

Cystic Fibrosis

Drug therapy in pediatric patients with cystic fibrosis has been reviewed.[52] For unknown reasons, these patients require increased doses of certain drugs. Studies have reported higher clearance of drugs, such as gentamicin, tobramycin, netilmicin, amikacin, dicloxacillin, cloxacillin, 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.[52] The severity of the illness may influence the change in dosage requirements, but this is not certain. Chapter 47 reviews these changes in detail.

Obesity

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 or greater than the 95th percentile.[53]

Obesity rates have been steadily increasing from 1999 to 2000 through 2017 to 2018 for children and adolescents aged 2 to 19 years. The obesity rate in 2017 to 2018 was 19.3% with an obesity prevalence of 13.4% among children 2 to 5 years of age, 20.3% for children 6 to 11 years of age and 21.2% among 12 to 19 years of age.[54–56] Rate of BMI increase in children 2 to 19 years of age nearly doubled during the Coronavirus disease pandemic compared to the prepandemic period. Obesity prevalence of 19.3% in persons 2 to 19 years of age prepandemic increased to 22.4% during the pandemic. The impact from stay-at-home orders and school closures resulted in a decline in physical activity and weight gain.[57,58] Interventions that promote healthy behavior such as weight management programs, food assistance that facilitates healthy eating, and exercise programs to increase physical activity are needed.

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.[59] During a 1999 to 2008 study period, 49% of overweight and 61% of obese adolescents had one or more cardiovascular risk factors, which included prehypertension or hypertension, low high-density lipoprotein cholesterol and high low-density lipoprotein cholesterol, and elevated fasting glucose concentration. Obese children are more likely to have early-onset puberty.[60]

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. BMI > 30 kg/m^2 was associated with worse event-free survival, disease-free survival, and overall survival.[61,62] Studies show that obesity can directly impair the antileukemia efficacy of first-line chemotherapeutic agents and accelerate leukemia progression.[63] Adipocytes attract acute lymphoblastic leukemia (ALL) cells to migrate closer to fat cells which absorb chemotherapy decreasing its exposure to the cancer cells. Adipocytes secrete asparagine, glutamine, and fatty acids that contribute to the survival of leukemia cells lessening the probability of the patient's survival.[64,65] 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 the 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.[66] 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.[67] Obesity is also associated with cancer mortality. Obesity is responsible for more than 90,000 cancer deaths/year in the United States.[68] However, obese patients who achieved normal or overweight status for greater than 50% of the treatment duration had outcomes comparable to those in normal or overweight individuals. Non-pharmacologic interventions of improving diet and exercise may increase chemotherapy efficacy and disease response by increasing circulatory adiponectin and reducing insulin resistance, decreasing fat gain in overweight/obese patients and reducing minimal residual disease for patients with acute lymphoblastic leukemia.[69,70]

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.[71] 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 value 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.

The Pediatric Pharmacy Association supports the following in determining initial empiric medication doses for overweight/obese children:

- Weight-based dosing should be used in patients <18 years of age who are <40 kg
- Children ≥40 kg: Use weight-based dosing unless the patient's dose exceeds the recommended maximum adult dose for the specific indication
- When possible, plasma drug concentration monitoring should be used to adjust dosing; few studies have been conducted to establish effective drug dosing information for obese children.[72,73]

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.[74]

Obesity may affect warfarin dosage requirements in pediatric patients. Obese pediatric patients had an increased time to reach therapeutic INR values with the use of institutional dosing guidelines.[75] Additional studies are needed to determine warfarin dosage requirements in obese versus nonobese pediatric patients.

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.[76]

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 (eg, celiac disease, gastroenteritis, and severe malabsorption) may require dosage adjustments.[43] Hypoxemia also has been shown to decrease the elimination of amikacin in low-birth-weight infants.[77] Critically ill adult and pediatric patients with severe head trauma require higher than normal doses of phenytoin in part because of increased intrinsic clearance.[78]

KEY ISSUES IN PEDIATRIC PHARMACOTHERAPY

Pain Management

7 For many years, the term *pain* could not be found in the index of any major pediatric medicine or pediatric surgical textbook.[79] 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, the results of these discoveries have been incorporated into clinical practice, making effective pain therapy a standard of pediatric care which must be adequately addressed as with the practice in adults.[80]

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, unmyelinated C fibers rather than along myelinated A-delta 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.[81] It is now known that previous pain experience leads to long-term consequences such as alterations in response to a subsequent painful event.[82] Taddio et al.[83,84] 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 (Table e20-1).[85–90]

TABLE e20-1

Techniques for Minimizing Pain Caused by Injection

Pharmacologic Methods	
EMLA[85]	*Advantages:* 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 >37 weeks' gestation. *Disadvantages:* Requires 1 hour before onset of adequate anesthesia, has a vasoconstrictive effect that may make starting IV catheters difficult, and may induce methemoglobinemia
J-tip with buffered lidocaine[86,91]	*Advantages:* Provides dermal anesthesia to a depth of 5-8 mm within 1-3 minutes; effective in decreasing the pain of IV cannulation *Disadvantage:* Makes a popping noise; this can scare a patient who is not properly prepared
Vapocoolant sprays (ethyl chloride or dichlorodifluoromethane)[87]	*Advantages:* 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 *Disadvantages:* Brief duration of action, so procedure should be completed in 1 or 2 minutes; may not be effective in reducing injection pain in infants aged 2-6 months
Local anesthetic (lidocaine)[88]	*Advantage:* Reduces the pain of subsequent needle insertion *Disadvantage:* Local anesthetic injection itself is associated with pain and burning sensation
Pacifier with sucrose[89]	*For preterm neonates:* 0.1-0.4 mL of a 12%-24% sucrose solution (place on pacifier or the tongue 2 minutes before procedure); *for term neonates:* 1-2 mL of a 12%-24% sucrose solution (place on pacifier or the tongue 2 minutes before procedure) *Advantage:* Noninvasive method to reduce pain associated with needle insertion in infants *Disadvantage:* Sucrose solution's effect in reducing pain gradually decreases over time; loses efficacy by 4-6 months of age
Other Techniques	
Site selection[90]	*For children older than 18 months:* Use of the deltoid muscle for IM injections is associated with less pain than injections administered in the thigh; *for children older than 3 years*: Use of the ventrogluteal area for injection is associated with less pain than the anterior thigh or dorsogluteal area
Z-tract technique	Z-tract IM injection technique is less painful (pull skin taut at the injection site, give injection, and then release the skin); use a higher-gauge needle when the injectable solution is not viscous
Behavioral	Use of distraction methods (eg, blowing bubbles, providing music by headphones, relaxation, imagery, self-hypnosis, or having parents present for the procedure) can be helpful

Virtual Reality[92]	Pediatric patients undergoing PIVC placement who received a Virtual Reality intervention experienced significantly less anxiety and pain compared to patients receiving standard care (simple distraction techniques [eg, music, coloring, singing, and talking] and the application of numbing cream)

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

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, patient-controlled analgesia, epidural anesthesia, peripheral nerve blockade, local anesthetics, liposomal bupivacaine via local infiltration for postsurgical local analgesia, nonsteroidal antiinflammatory drugs, different routes for traditional agents (ie, transmucosal and transdermal), and nonopioid adjuvant drugs (Table e20-2).[93–98] Opioids are frequently prescribed for children after surgery but evidence-based guidelines for opioid prescribing in children to provide optimal postoperative pain management are lacking. Best practice concepts like standardizing opioid dosing strategies that are age and procedure specific, and use of multimodal and opioid-sparing regimens have been difficult to implement due to the challenging nature of managing pain, as well as balancing the prevention of drug diversion and opioid abuse. Opioid-prescribing guidelines for safer postoperative pain management in children and adolescents have been developed to minimize risks associated with opioid use and maximize nonopioid regimens.[99] Pain management techniques, education, research, developmentally appropriate pain assessment scales, implementation of opioid and pain stewardship programs and increasing awareness of pain management options have helped to improve the quality of life in children.

TABLE e20-2

Opioid Administration for Acute and Severe Pain

Intermittent IV or PO bolus administration (not as needed)	In 2018, the FDA announced limiting use of prescription opioid cough and cold medications containing codeine or hydrocodone in children <18 years old. Weak opioids (eg, codeine, hydrocodone, and 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 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, then use the lowest effective dose for the shortest period of time on an as-needed basis.[100] 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 concentrations, so the patient may alternate between peak blood concentrations associated with untoward effects and trough concentrations 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.
IV continuous infusion[93,94]	Loading dose is administered to rapidly achieve a therapeutic blood concentration and pain relief (ie, morphine loading dose of 0.05-0.15 mg/kg in children; 0.1 mg/kg infused over 90 minutes in neonates). Loading dose is followed by a maintenance continuous infusion. Doses that are considered safe in children can cause respiratory depression and seizures in neonates because of decreased clearance, immature blood–brain barrier at birth that is more permeable to morphine, and an increased unbound fraction of morphine that increases CNS effects of the drug.
PCA[95]	Gives patient some control over his or her pain therapy. PCA allows the patient to self-administer small opioid doses. The PCA-Plus (Abbott, Chicago, IL) pump allows the patient to receive a continuous infusion together with a set number of self-administered doses per hour. PCA helps to eliminate wide peak and trough fluctuations so that blood concentrations remain in a therapeutic range. Children as young as 5 or 6 years of age can master the use of PCA.
Epidural and intrathecal analgesia[96]	Effective in the management of severe postoperative, chronic, or cancer pain. Spinal opioids can be administered by a single bolus injection into the epidural or subarachnoid space or by continuous infusion via an indwelling catheter. Dosage requirement by these routes is significantly less than with IV administration. Morphine, hydromorphone, fentanyl, and sufentanil are effective when administered intrathecally. Bupivacaine is the most commonly used local anesthetic in continuous epidural infusions. Fentanyl, morphine, or hydromorphone usually is combined with bupivacaine for epidural infusions. Transdermal administration. Fentanyl and buprenorphine are available as a transdermal formulation. Multiple patches of an agent may be applied for patients who require higher doses. Disadvantage of transdermal administration is the requirement for an alternative short-acting opioid for break-through pain.
Transmucosal administration	Fentanyl lozenge is absorbed transmucosally. It is useful for providing analgesia during painful procedures. Advantages include rapid onset of action (within 15 minutes), short duration of action (60-90 minutes), and painless administration because no injection is needed. Common side effects are vomiting and mild to moderate oxygen desaturation. Doses of 10-15 µg/kg provide blood concentrations equivalent to 3-5 µg/kg IV.

FDA, Food and Drug Administration; IM, intramuscular; NSAID, nonsteroidal antiinflammatory drug; PO, by mouth; PCA, patient-controlled analgesia.

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.

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, diazepam, digoxin, fentanyl, 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 with digoxin[101] and morphine[102] in infants. One solution to this problem is to dilute these concentrated products, but such alterations can influence the stability or compatibility of these drugs. Because of limited data, pharmacists justifiably may be reluctant to alter dosage forms of certain drugs.

Selection of the appropriate vehicle to dilute the adult dosage forms for use in pediatric patients can be difficult. Phenobarbital sodium contains propylene glycol in the original product to improve drug stability. As propylene glycol can cause hyperosmolality in infants,[37] further addition of this vehicle may not be wise. Because of limited access to IV sites in pediatric patients, drugs must be administered through the same site; however, data on drug compatibilities often are missing. Newborn infants often require aminoglycosides for presumed or proven sepsis and calcium gluconate for correction of hypocalcemia or calcium supplementation. Tobramycin and calcium gluconate were compatible, at least during a 1-hour administration at the same site.[102]

Administration of oral drugs continues to challenge parents and nurses. Alteration of these drugs by crushing or mixing, refusal of patients to accept the medication, and loss of drug during administration are some factors that can affect pediatric therapy. A common practice is to mix medications in applesauce, syrup, ice cream, or other vehicles just before administration to make the drugs palatable. In 2015, the FDA has approved levetiracetam (Spritam) that uses 3D printing technology, paving the way for potential customization of drugs to meet the needs of pediatric patients. It uses a delivery system that creates premeasured doses which disintegrate in the mouth with a small volume of liquid.

A number of extemporaneous formulations for oral, IV, and rectal administration are included in a compilation of products for use in pediatric patients.[103] 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 (eg, sodium valproate and morphine) can be administered rectally to infants who have limited access for IV drug administration or if oral drug administration cannot be accomplished.

Flexibility of Dosage Forms

Factors including age, health condition, indication for use, ability to take the medication, availability of various dosage forms, and patient or caregiver preference should be considered in selecting an optimal dosage form for patients. As example, oral medications may be administered in many forms including drops, liquid, tablets (eg, regular, chewable, disintegrating or film), granules and capsules. Some medications are available in multiple flavors including cherry, strawberry, grape, banana, bubble gum and orange.

Transdermal drug delivery can be used in pediatric patients (a) to avoid problems of drug absorption from the oral route and complications from the IV route and (b) 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. However, the commercially available transdermal dosage forms (eg, 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.[104]

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 (eg, 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.[105] Studies in pediatric volunteers have compared the palatability of antibiotics,[106] 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 (eg, 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 (eg, 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 generally 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 four decades.[54,55] 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.[107,108] 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 (eg, IV immunoglobulin, infliximab, rituximab, and liposomal amphotericin B [AmBisome]) can be difficult.

It should be realized that estimation of dose requirements based on scaling with body weight or surface area assumes linear growth and maturation affecting pharmacokinetics and pharmacodynamics. This assumption may not be valid across all age groups ranging from premature newborns to 18 years old. Thus, optimal dosage requirements should be determined from the findings of pharmacokinetics, pharmacodynamics, efficacy, and safety studies in specific pediatric cohorts. There is also a need to identify appropriate biomarkers that may reflect desired clinical endpoints specifically in the pediatric population, since inconsistent findings may be observed in pediatric patients versus adults. For example, unlike systolic blood pressure in adults with hypertension, diastolic blood pressure may be a preferred age-appropriate pharmacodynamic/response biomarker in pediatric patients with hypertension.[109]

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 gave a complementary or alternative treatment 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 US 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.[110]

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.

Marijuana has been used in pediatric patients with life-limiting or severely debilitating conditions (eg, cancer and epilepsy) when other treatments were ineffective. In 2018, cannabidiol (Epidiolex®) was the first FDA-approved cannabis-based drug marketed to treat two forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome in patients ≥ 2 years of age. It was classified as a Schedule V prescription drug.[111,112] A 2015 policy statement of AAP cited several studies documenting the adverse effects of marijuana in adolescents.[113] These have included impaired learning due to decreased short-term memory, attention span and problem solving ability; risks with motor vehicle driving associated with changes in motor control, coordination, judgment, and tracking ability; brain development; and drug dependence or addiction which may develop later in adulthood. AAP recommended that research and development under FDA regulations be continued to demonstrate short-term and long-term effectiveness and safety of cannabidiol among children and adolescents.

Breakthrough Therapies

Gene therapy is being used to provide better outcomes and potential curative therapies at the patient level for diseases not previously treatable. Use of new gene correction technologies such as gene editing and gene silencing, replacing faulty genes, as well as using viruses to insert genes into blood-forming stem cells are part of the strategy of delivering breakthrough therapies.[99] Survival rate for pediatric ALL is ~80% to 90% with standard chemotherapy. Relapsed ALL is the leading cause of cancer deaths in children. Tisagenlecleucel is a chimeric antigen receptor T-cell (CAR-T) therapy that simultaneously serves as cell therapy, gene therapy and immunotherapy. The drug was approved by the FDA for patients 3 to 25 years of age with B-cell precursor ALL that is refractory to treatment or for patients who experience relapse. Up to 75% of patients with refractory disease are alive at 1-year after CAR-T therapy with more than 60% cured.[114–116]

The FDA approved voretigene neparovec-rzyl, the first gene therapy for the treatment of patients ≥12 months of age with confirmed biallelic RPE65 mutation-associated retinal dystrophy, a disease caused by mutation in a specific gene. Voretigene neparovec-rzyl works by sending a normal copy of the RPE65 gene directly to retinal cells, which can then produce the enzyme essential for normal vision.[117]

Spinal muscular atrophy (SMA) is caused by mutations in the survival motor neuron gene which results in loss of alpha motor neurons in the spinal cord. SMA (type 1) is the leading cause of death from genetic disease in infants who ultimately develop respiratory failure. Median survival is 6 to 8 months in treatment-naïve patients with SMA type 1. Onasemnogene abeparvovec, a recombinant adeno-associated virus serotype 9 vector gene replacement therapy, delivers a functional copy of the human SMN gene that crosses the blood–brain barrier after a single intravenous infusion. All patients in the therapeutic-dose cohort of the START phase 1 trial were alive without the need of permanent ventilation at 24 months of age. A long-term ongoing follow-up study at the therapeutic-dose showed a durable response in patients which was maintained up to 6.2 years after dosing.[118]

Medication Safety

10 The Institute of Medicine reported that between 44,000 and 98,000 Americans each year die as a result of medical errors in hospitals.[119] 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.[120–122] 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.[123] 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).[124–128] In 2008, The Joint Commission issued an alert on preventing errors related to commonly used anticoagulants.[129] 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.[124] 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 provider order entry systems with clinical decision support and dosing alerts, 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.[122,124–126,130] 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 (see Chapter e4).

Pharmacogenomics and Medication Prescribing

Since most currently used drugs are prescribed as "one size fits all" without knowledge and/or application of adequate pharmacogenomic data from pediatric patients, this approach can potentially lead to subtherapeutic response or toxicity, in part due to the presence of genomic variants in certain patients (see Chapter e7). Pharmacogenomic research is needed to understand the influence of genes on drug response to determine effective and safe medications and doses, specific to an individual patient's genotype. Although most of the information is derived from studies done in adults, the Food and Drug Administration updates the "Table of Pharmacogenomic Biomarkers in Drug Labeling" and "Table of Pharmacogenetic Associations" to consider an increasing role of pharmacogenomics in drug prescribing.[131,132] Of the 308 drug-gene pairs identified, 36% were associated with a biomarker defined drug indication, 33% with polymorphic drug metabolism, and 28% with susceptibility to adverse drug reactions. This type of information may guide prescribing decisions to improve the use of medications in pediatric patients.[133]

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, has not been studied for most drugs. The effect of these factors on the development of CYP isozymes (eg, CYP3A4, CYP2D6, CYP1A2, CYP2C9, and CYP2C19), other enzymes, and P-glycoprotein needs to be studied (see Chapters e6 and e7). Targeted precision therapy matched to molecular alterations identified by tumor profiling offers possibility for improved treatment in pediatric cancer. Similarly, comparative efficacy and safety data for many therapies are unavailable. Studies on the influence of pharmacogenomics on drug therapy to achieve optimal clinical and economic outcomes and quality of life in pediatric patients are needed.

The development of new drugs has contributed to improved patient care. Food and Drug Administration regulations 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 emphasis 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 vaccinations. 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 harmful substances including alcohol, smoking, and drugs during pregnancy may decrease mortality rates as well as morbidity from illnesses, including acquired immunodeficiency syndrome.

Finally, efforts should be made to offer evidence-based pharmacotherapy. 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-risk and high-cost drugs.

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

ABBREVIATIONS

6-MP	6-mercaptopurine
AAP	American Academy of Pediatrics
ADHD	attention-deficit/hyperactivity disorder
ALL	acute lymphoblastic leukemia
BMI	body mass index
BSA	body surface area
CAR-T	chimeric antigen receptor T-cell therapy
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
SMA	spinal muscular atrophy
SSRI	selective serotonin reuptake inhibitor
TPMT	thiopurine *S*-methyltransferase
USP	United States Pharmacopeia
V_D	volume of distribution

REFERENCES

1. Reproductive Health. Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion. CDC Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/reproductivehealth/MaternalInfantHealth/InfantMortality.htm Accessed on September 16, 2021.

2. Avery GB, Randolph JG, Weaver T. Gastric acidity in the first day of life. *Pediatrics*. 1966;37:1005–1007. [PubMed: 5949019]

3. Agunod M, Yamaguchi N, Lopex R, et al. Correlative study of hydrochloric acid, pepsin, and intrinsic factor secretion in newborns and infants. *Am J Dig Dis.* 1969;14:400–414. [PubMed: 4892100]

4. Huang NN, High RN. Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups. *J Pediatr.* 1953;42:657–668. [PubMed: 13053366]

5. Silverio J, Poole JW. Serum concentrations of ampicillin in newborn infants after oral administration. *Pediatrics*. 1973;51:578–580. [PubMed: 4196554]

6. O'Connor WJ, Warren GH, Edrada LS, et al. Serum concentrations of sodium nafcillin in infants during the perinatal period. *Antimicrob Agents Chemother.* 1965;5:220–222.

7. Jalling B. Plasma concentrations of phenobarbital in the treatment of seizures in newborns. *Acta Paediatr Scand.* 1975;64:514–524. [PubMed: 1155069]

8. Kearns GL, Abdel-Rahman SM, Alander SW, et al. Drug therapy: Developmental pharmacology—Drug disposition, action, and therapy in infants and children. *N Engl J Med.* 2003;349:1157–1167. [PubMed: 13679531]

9. Signer E, Fridrich R. Gastric emptying in newborns and young infants. *Acta Paediatr Scand.* 1975;64:525–530. [PubMed: 1155070]

10. Boreus IO. Plasma concentrations of phenobarbital in mother and child after combined prenatal and postnatal administration for prophylaxis of hyperbilirubinemia. *J Pediatr.* 1978;93:695–698. [PubMed: 702253]

11. Morselli PL. Serum levels and pharmacokinetics of anticonvulsants in the management of seizure disorders. In: Merkin B, ed. *Clinical Pharmacology*. Chicago: Mosby; 1978:89.

12. Tyrala FF, Hillman LS, Hillman RE, et al. Clinical pharmacology of hexa-chlorophene in newborn infants. *J Pediatr.* 1977;91:481–486. [PubMed: 894425]

13. McFadden S, Haddow JE. Coma produced by topical application of isopropanol. *Pediatrics*. 1969;43:622–623. [PubMed: 5777081]

14. Evans NJ, Rutter N, Hadgraft J, et al. Percutaneous administration of theophylline in preterm infant. *J Pediatr.* 1985;107:307–311. [PubMed: 4020561]

15. Friis-Hansen B. Body water compartments in children: Changes during growth and related changes in body composition. *Pediatrics*. 1961;28:169–181. [PubMed: 13702099]

16. Haughey DB, Hilligoss DM, Grassi A, et al. Two-compartment gentamicin pharmacokinetics in premature neonates: A comparison to adults with decreased glomerular filtration rates. *J Pediatr.* 1980;96:325–330. [PubMed: 7351607]

17. Nahata MC, Powell DA, Durrell DE, et al. Effect of gestational age and birth weight on tobramycin kinetics in newborn infants. *J Antimicrob Chemother.* 1984;14:59–65. [PubMed: 6480541]

18. Roberts RJ. Pharmacologic principles in therapeutics in infants. *Drug Therapy in Infants: Pharmacologic Principles and Clinical Experience*. Philadelphia, PA: WB Saunders; 1984:3–12.

19. Pitlick W, Painter M, Pippenger C. Phenobarbital pharmacokinetics in neonates. *Clin Pharmacol Ther.* 1978;23:346–350. [PubMed: 627141]

20. Painter MJ, Pippenger C, MacDonald H, et al. Phenobarbital and diphenylhydantoin levels in neonates with seizures. *J Pediatr.* 1978;92:315–319. [PubMed: 621616]

21. Silverman WA, Anderson DH, Blanc WA, et al. A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens. *Pediatrics*. 1956;18:614–624. [PubMed: 13370229]

22. Odell GB. The dissociation of bilirubin from albumin and its clinical implications. *J Pediatr.* 1959;55:268–279. [PubMed: 14428276]

23. Morselli PL. Clinical pharmacokinetics in neonates. *Clin Pharmacokinet.* 1976;1:81–98. [PubMed: 13955]

24. Committee on Drugs, American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108:776–789. [PubMed: 11533352]

25. Dinh J, Brown JT, Abdel-Rahman S. Pediatric pharmacokinetics. *Pediatric Pharmacother.* 2020;2:33–50.

26. Rane A. Drug metabolism and disposition in infants and children. In: Yaffe JF, ed. *Neonatal and Pediatric Pharmacology: Therapeutic Principles in Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:32–43.

27. Weiss CF, Glazko AJ, Weston JK. Chloramphenicol in the newborn infant: A physiologic explanation of its toxicity when given in excessive doses. *N Engl J Med.* 1960;262:787–794. [PubMed: 13843700]

28. Nahata MC, Powell DA. Comparative bioavailability and pharmacokinetics of chloramphenicol after intravenous chloramphenicol succinate in premature infants and older patients. *Dev Pharmacol Ther.* 1983;6:23–32. [PubMed: 6839912]

29. Kuhn R, Nahata MC, Powell DA, et al. Netilmicin pharmacokinetics in newborn infants. *Eur J Clin Pharmacol.* 1986;29:635–637. [PubMed: 3956569]

30. Cha PCW, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. *Clin Pharmacol Ther.* 1992;51:334–342. [PubMed: 1544290]

31. Edwards DJ, Zarowitz BJ, Slaughter RL. Theophylline. In: Evans WE, Schentag JJ, Jusko WJ, eds. *Applied Pharmacokinetics*. 3rd ed. Vancouver, WA: Lippincott Williams & Wilkins; 1992:1–47.

32. Takahashi H, Ishikawa S, Nomoto S, et al. Developmental changes in pharmacokinetics and pharmacodynamics of warfarin enantiomers in Japanese children. *Clin Pharmacol Ther.* 2000;68:541–555. [PubMed: 11103757]

33. Lambert GH, Schoeller DA, Kotake AN, et al. The effect of age, gender, and sexual maturation on the caffeine breath test. *Dev Pharmacol Ther.* 1986;9:375–388. [PubMed: 3102191]

34. McLeod HL, Krynetski ER, Relling MV, Evans WE. Genetic polymorphism of thiopurine methyltransferase and its clinical relevance for childhood acute lymphoblastic leukemia. *Leukemia*. 2000;14:567–572. [PubMed: 10764140]

35. 2020 Focused Updates to the Asthma Management Guidelines, US Department of Health and Human Services, National Heart, Lung and Blood Institute. Available at: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines. Accessed on September 16, 2021.

36. Kearin M, Kelly JG, O'Malley K. Digoxin "receptors" in neonates: An explanation of less sensitivity to digoxin than in adults. *Clin Pharmacol Ther.* 1980;28:346–349. [PubMed: 7408394]

37. Kawai M, Momoi T, Yorifuji T, et al. Unfavorable effects of growth hormone therapy on the final height of boys with short stature not caused by growth hormone deficiency. *J Pediatr.* 1997;130:205–209. [PubMed: 9042121]

38. U.S. Food and Drug Adminsitration. Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. Available at: https://www.fda.gov/media/85072/download. Accessed on March 7, 2022.

39. Glasgow AM, Boeckx RL, Miller MK, et al. Hyperosmolality in small infants due to propylene glycol. *Pediatrics*. 1983;72:353–355. [PubMed: 6889040]

40. Hiller JL, Benda GI, Rahatzad M, et al. Benzyl alcohol toxicity: Impact of mortality and intraventricular hemorrhage among very low birth weight infants. *Pediatrics*. 1986;77:500–506. [PubMed: 3515306]

41. Grossman ER, Walchek A, Freedman H. Tetracyclines and permanent teeth: The relation between dose and tooth color. *Pediatrics*. 1971;47:567–570. [PubMed: 4993997]

42. American Academy of Pediatrics Committee on Infectious Diseases. The use of systemic and topical fluoroquinolones, policy statement. *Pediatrics*. 2016;138(5):e20162706. [PubMed: 27940800]

43. Kauffman RE, Habersange R. Modification of dosage regimens in disease states of childhood. In: Mirking BL, ed. *Clinical Pharmacology and Therapeutics: A Pediatric Perspective*. Chicago: Mosby Year Book; 1978:73–88.

44. Roberts RJ. Special considerations in drug therapy in infants. *Drug Therapy in Infants: Pharmacologic Principles and Clinical Experience*. Philadelphia, PA: WB Saunders; 1984:25–35.

45. Feinstein RA, Miles MV. The effect of acute viral hepatitis on theophylline clearance. *Clin Pediatr.* 1985;24:357–358.

46. Hogg RJ, Furth S, Lemley KV, et al. National Kidney Foundation's kidney disease outcomes quality initiative clinical practice guidelines for chronic kidney disease in children and adolescents: Evaluation, classification, and stratification. *Pediatrics*. 2003;111:1416–1421. [PubMed: 12777562]

47. Schwartz Gj, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children and adolescents. *Pediatr Clin North Am.* 1987;34:571–590. [PubMed: 3588043]

48. Schwartz GJ, Furth SL. Glomerular filtration rate measurement and estimation in chronic kidney disease. *Pediatr Nephrol.* 2007;22:1839–1848. [PubMed: 17216261]

49. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. *J Am Soc Nephrol.* 2009;20:629–637. [PubMed: 19158356]

50. Lemley KV. Estimating GFR in children: Schwartz redux. *Nature Rev Nephrol.* 2009;5:310–311.

51. Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol.* 2009;4:1832–1843. [PubMed: 19820136]

52. Wallace CS, Hall M, Kuhn RJ. Pharmacologic management of cystic fibrosis. *Clin Pharm.* 1993;12:657–674. [PubMed: 8306566]

53. Centers for Disease Control and Prevention. About Child & Teen BMI. Atlanta, GA: Centers for Disease Control and Prevention. 2015. Available at: http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html. Accessed on March 7, 2022.

54. Centers for Disease Control and Prevention. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2-19 years: United States, 1963-1965 through 2017-2018. NCHS Health E-Stats, National Center for Health Statistics. 2020. Available at: https://www.cdc.gov/nchs/data/hestat/obesity-child-17-18/obesity-child.htm. Accessed Macrh 7, 2022.

55. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007–2008. *JAMA.* 2010;303:242–249. [PubMed: 20071470]

56. Li HL, Tsoi MF, Feng Q, et al. Prevalence of childhood obesity in the United States, 1999-2018: A 20 year analysis. *J Endocr Soc.* 2021;5(Supp 1):A24–25.

57. An R. Projecting the impact of the coronavirus disease-2019 pandemic on childhood obesity in the United States: A microsimulation model. *J Sport Health Sci.* 2020;9:302–312. [PubMed: 32454174]

58. Lange SJ, Kompaniyets L, Freedman DS, et al. Longitudinal trends in body mass index before and during the COVID-19 pandemic among persons aged 2-19 years- United States, 2018-2020. *MMWR Morb Mortal Wkly Rep.* 2021;70:1278–1283. [PubMed: 34529635]

59. Speiser PW, Rudolf MCJ, Anhalt H, et al. Consensus statement: Childhood obesity. *J Clin Endocrinol Metab.* 2005;90(3):1871–1887. [PubMed: 15598688]

60. May AL, Kuklina EV, Yoon PW. Prevention of cardiovascular disease risk factors among US adolescents, 1999-2008. *Pediatrics*. 2015;129:1035–1041.

61. Butturini AM, Dorey FJ, Lange BJ, et al. Obesity and outcome in pediatric acute lymphoblastic leukemia. *J Clin Oncol.* 2007;25:2063–2069. [PubMed: 17513811]

62. Stock W, Luger SM, Advani AS, et al. A pediatric regimen for older adolescents and young adults with acute lymphoblastic leukemia: Results of CALGB 10403. *Blood*. 2019;133:1548–1559. [PubMed: 30658992]

63. Behan JW, Yun JP, Proektor MP, et al. Adipocytes impair leukemia treatment in mice. *Cancer Res.* 2009;69:7867–7874. [PubMed: 19773440]

64. Mittelman SD. Childhood obesity and leukemia: Opportunities for intervention. AACR International Conference on Frontiers in Cancer Prevention Research; Sept 30, 2014.

65. Pramanik R, Sheng X, Ichihara B, et al. Adipose tissue attracts and protects acute lymphoblastic leukemic cells from chemotherapy. *Leuk Res.* 2013;37:503–509. [PubMed: 23332453]

66. Hijiya N, Panetta JC, Zhou Y, et al. Body mass index does not influence pharmacokinetics or outcome of treatment of children with acute lymphoblastic leukemia. *Blood*. 2006;108:3997–4002. [PubMed: 16917005]

67. Griggs JJ, Mangy PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology Practice Guidelines 2012. *J Clin Oncol.* 2012;30:1–12. [PubMed: 22105825]

68. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003; 348:1625–1638. [PubMed: 12711737]

69. Orgel E, Sposto R, Malvar J, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: A report from the Children's Oncology Group. *J Clin Oncol.* 2014;32:1331–1337. [PubMed: 24687836]

70. Orgel E, Framson C, Buxton R, et al. Caloric and nutrient restriction to augment chemotherapy efficacy for acute lymphoblastic leukemia: The IDEAL trial. *Blood Adv.* 2021;5:1853–1861. [PubMed: 33792627]

71. Kendrick JG, Carr RR, Ensom MHH. Pediatric obesity: Pharmacokinetics and implications for drug dosing. *Clin Ther.* 2015;37:1897–1923. [PubMed: 26361823]

72. Wurtz R, Itokazu G, Rodvold K. Antimicrobial dosing in obese patients. *Clin Infect Dis.* 1997;25:112–118. [PubMed: 9243045]

73. Matson KL, Horton ER, Capino AC. Medication dosage in overweight and obese children. *J Pediatr Pharmacol Ther.* 2017;22:81–83. [PubMed: 28337087]

74. Miller M, Miller JL, Hagemann TM, et al. Vancomycin dosage in overweight and obese children. *Am J Health-Syst Pharm.* 2011;68:2062–2068. [PubMed: 22011985]

75. Moffett BS, Bomgaars LR. Response to warfarin therapy in obese pediatric patients dosed according to institutional guidelines. *J Pediatr Hematol Oncol.* 2014;36:e487–e489. [PubMed: 24458250]

76. Olutoye OA, Yu X, Govindan K, et al. The effect of obesity on the ED95 of propofol for loss of consciousness in children and adolescents. *Anesth Analg.* 2012;115:147–153. [PubMed: 22575569]

77. Myers MG, Roberts JF, Mirhig NJ. Effect of gestational age, birth weight, and hypoxemia on the pharmacokinetics of amikacin in serum of infants. *Antimicrob Agents Chemother.* 1977;11:1027–1032. [PubMed: 879747]

78. Bahal-O'Mara N, Jones R, Nahata MC, et al. Pharmacokinetics of phenytoin in children with acute neurotrauma. *Crit Care Med.* 1995;23:1418–1424. [PubMed: 7634814]

79. Rana SR. Pain: A subject ignored [letter]. *Pediatrics*. 1987;79:309–310. [PubMed: 3808811]

80. Franch LS, Greenberg CS, Stevens B. Pain assessment in infants and children. *Pediatr Clin North Am.* 2000;47:487–512. [PubMed: 10835987]

81. American Academy of Pediatrics Committee on Fetus and Newborn, American Academy of Pediatrics Section on Surgery, Canadian Paediatric Society Fetus and Newborn Committee, Batton DG, Barrington KJ, Wallman C. Prevention and management of pain in the neonate: An update. *Pediatrics*. 2006;118:2231–2241. [PubMed: 17079598]

82. Fitzgerald M, Howard RF. The neurobiologic basis of pediatric pain. In: Schechter NL, Berde CB, Yaster M, eds. *Pain in Infants, Children, and Adolescents*. Baltimore, MD: Lippincott Williams & Wilkins; 2003:19–42.

83. Taddio A, Katz J, Ilersich Al, et al. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet*. 1997;349:559–603.

84. Taddio A, Ohlsson A, Einarson T, et al. A systematic review of lidocaine-prilocaine cream for neonatal circumcision pain. *N Engl J Med.* 1997;336:1197–1201. [PubMed: 9110906]

85. Uhari M. Eutectic mixture of lidocaine and prilocaine for alleviating vaccination pain in infants. *Pediatrics*. 1993;92:719–721. [PubMed: 8414863]

86. Zempsky WT. Pharmacologic approaches for reducing venous access pain in children. *Pediatrics*. 2008;122:S140–S153. [PubMed: 18978008]

87. Reis EC, Holobukov R. Vapocoolant spray is equally effective as EMLA cream in reducing immunization pain in school aged children. *Pediatrics*. 1997;100:5.

88. Bartfield JM, Connis P, Barbera J, et al. Buffered versus plain lidocaine as a local anesthetic for simple laceration repair. *Ann Emerg Med.* 1990;19:1387–1390. [PubMed: 2240750]

89. Schechter NL, Berde CB, Yaster M, et al. The pain (and stress) in infants in a neonatal intensive care unit. In: Wong CM, McIntosh N, Menon G, Franck LS, eds. *Pain in Infants, Children, and Adolescents*. Baltimore, MD: Lippincott Williams & Wilkins; 2003:669–692.

90. Keen MF. Comparison of intramuscular injection techniques to reduce site discomfort and lesions. *Nurs Res.* 1986;35:207–210. [PubMed: 3636818]

91. Spanos S, Booth R, Koenig H, et al. Jet injection of 1% buffered lidocaine versus topical ELA-Max for anesthesia before peripheral intravenous catheterization in children: A randomized controlled trial. *Pediatr Emerg Care*. 2008;24:511–515. [PubMed: 18645542]

92. Gold JI, SooHoo M, Laikin AM, et al. Effect of an immersive virtual reality intervention on pain and anxiety associated with peripheral intravenous catheter placement in the pediatric setting: a randomized clinical trial. *JAMA Network Open*. 2021;4:e2122569. [PubMed: 34432011]

93. Golianu B, Krane EJ, Galloway KS, et al. Pediatric acute pain management. *Pediatr Clin North Am.* 2000;47:559–587. [PubMed: 10835991]

94. Chay PCW, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationship of morphine in neonates. *Clin Pharmacol Ther.* 1992;51:334–342. [PubMed: 1544290]

95. Berde CB, Lehn BM, Yee JD, et al. Patient-controlled analgesia in children and adolescents: A randomized, prospective comparison with intramuscular administration of morphine for postoperative analgesia. *J Pediatr.* 1991;118:460–466. [PubMed: 1999793]

96. Nichols DG, Yaster M, Lynn AM, et al. Disposition and respiratory effects of intrathecal morphine in children. *Anesthesiology*. 1993;79:733–738. [PubMed: 8214752]

97. Zempsky WT, Schechter NL. What's new in the management of pain in children. *Pediatr Rev.* 2003;24:337–348. [PubMed: 14523160]

98. Suresh S, Birmingham PK, Kozlowski RJ. Pediatric pain management. *Anesthesiol Clin.* 2012;30:101–117. [PubMed: 22405436]

99. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. *N Engl J Med.* 2015;373:1541–1552. [PubMed: 26465987]

100. Kelly LE, Rieder M, van den Anker J, et al. More codeine fatalities after tonsillectomy in North American children. *Pediatrics*. 2012;129:1343–1347.

101. Berman W, Whitman V, Marks KH, et al. Inadvertent overadministration of digoxin to low birth weight infants. *J Pediatr.* 1978;92:1024–1025. [PubMed: 660345]

102. Zenk KE, Anderson S. Improving the accuracy of minivolume injections. *Infusion*. 1982;Jan-Feb:7–11.

103. Nahata MC, Pai V. *Pediatric Drug Formulations*. 7th ed. Cincinnati, OH: Harvey Whitney Books; 2019:1–507.

104. Martin AJ, Campbell DA, Gluyas PA, et al. Characteristics of near-fatal asthma in childhood. *Pediatr Pulmonol.* 1995;20:1–8. [PubMed: 7478775]

105. Erglin A, Frattarelli DAC. Compliance with pediatric medication regimens. In: Yaffe SJ, ed. *Pediatric Pharmacology: Therapeutic Principles in Practice*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:60–68.

106. Matsui D, Barron A, Rieder MJ. Assessment of the palatability of antistaphylococcal antibiotics in pediatric volunteers. *Ann Pharmacother.* 1996;30:586–588. [PubMed: 8792942]

107. Cheymol G. Effects of obesity on pharmacokinetics: Implications for drug therapy. *Clin Pharmacokinet.* 2000;39:215–231. [PubMed: 11020136]

108. Miller JL. Evaluation of inpatient admissions and potential antimicrobial and analgesic dosing errors in overweight children. *Ann Pharmacother.* 2010;44:35–42. [PubMed: 20028958]

109. Mulugeta Y, Zajicek A, Barrett J, et al. Development of drug therapies for newborns and children the scientific and regulatory imperatives. *Pediatr Clin N Am.* 2017;64:1185–1196.

110. Lanski SL, Greenwald M, Perkins A, et al. Herbal therapy use in a pediatric emergency department population: Expect the unexpected. *Pediatrics*. 2003;111:981–985. [PubMed: 12728075]

111. Devinsky O, Cross JH, Wright S. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med.* 2017;377:699–700. [PubMed: 28813226]

112. Thiele EA, Marsh ED, French JA et al. Cannabidiol in patients with seizures associated with Lenox-Gastaut syndrome (GUPCARE4): A randomised, double-blind placebo-controlled phase 3 trial. *Lancet*. 2018;391:1085–96. [PubMed: 29395273]

113. American Academy of Pediatrics. Policy Statement: The impact of marijuana policies on youth: Clinical, research and legal update. *Pediatrics*.

2015;135:1–4. [PubMed: 25548323]

114. U.S. Food and Drug Adminsitration. FDA approval brings first gene therapy to the United States CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia. Available at: https://www.fda.gov/news-events/press-announcements/fda-approval-brings-first-gene-therapy-united-states. Accessed on March 7, 2022.

115. Pulsipher M, Buechner J, Grupp SA, Maude SL, et al. Global registration trial of efficacy and safety of CTL019 in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia: Update to the interim analysis. *Clin Lymphoma Myeloma Leuk.* 2017;17:S263–S264.

116. Maude SL, Teachey DT, Porter DL, et al. CD19-targeted chimeric antigen receptor T-cell therapy for acute lymphoblastic leukemia. *Blood*. 2015;125:4017–4023. [PubMed: 25999455]

117. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvove (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: A randomized, controlled, open-label, phase 3 trial. *Lancet*. 2017;390:849–860. [PubMed: 28712537]

118. Mendell JR, Al-zaidy SA, Lehman KJ, et al. Five-year extension results of the phase I START trial of onasemnogene abeparvovec in spinal muscular atrophy. *JAMA Neurol.* 2021;78:834–841. [PubMed: 33999158]

119. Institute of Medicine, Committee on Quality of Health Care in American. *To Err is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 2000.

120. Raju TN, Kecskes S, Thornton JP, et al. Medication errors in neonatal and paediatric intensive-care units. *Lancet*. 1989;2:374–376. [PubMed: 2569561]

121. Folli HL, Poole RL, Benitz WE, et al. Medication error prevention by clinical pharmacists in two children's hospitals. *Pediatrics*. 1987;79:718–722. [PubMed: 3575028]

122. Kaushal R, Bates DW, Landrigan C, et al. Medication errors and adverse drug events in pediatric inpatients. *JAMA.* 2001;285: 2114–2120. [PubMed: 11311101]

123. USP Center for the Advancement of Patient Safety. *USP Issues Recommendations for Preventing Medication Errors in Children*. Rockville, MD: United States Pharmacopeia; 2003.

124. American Academy of Pediatrics Committee on Drugs and Committee on Hospital Care. Prevention of medication errors in pediatric inpatient setting. *Pediatrics*. 2003;112:431–436. [PubMed: 12897304]

125. Agency for Healthcare Research and Quality. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices*. AHRQ Publication No. 01-E058. Washington, DC: Agency for Healthcare Research and Quality; 2001.

126. Larsen GY, Parker HB, Cash J, et al. Standard drug concentrations and smart-pump technology reduce continuous-medication-infusion errors in pediatric patients. *Pediatrics*. 2005;116:21–25.

127. Sauberan JB, Dean LM, Fiedelak J, et al. Origins of and solutions for neonatal medication-dispensing errors. *Am J Health System Pharm.* 2010;67:49–57.

128. Arimura J, Poole RL, Jeng M, et al. Neonatal heparin overdose: A multidisciplinary team approach to medication error prevention. *J Pediatr Pharmacol Ther.* 2008;13:96–98. [PubMed: 23055872]

129. Joint Commission Sentinel Event Alert. Preventing errors relating to commonly used anticoagulants. Oakbrook Terrace, IL: The Joint Commission; 2008:41.

130. Stultz JS, Nahata MC. Complexities of clinical decision support illustrated by pediatric dosing alerts. *Ann Pharmacother.* 2015;49:1261–4. [PubMed: 26341414]

131. Table of pharmacogenomic biomarkers in drug labeling. US Food and Drug Administration. Availabile at: https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling. Accessed on September 16, 2021.

132. Table of pharmacogenetic associations. US Food and Drug Administration. Available at: https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations. Accessed on September 16, 2021.

133. Cheng CM, So TW, Bubp JL. Characteristics of pharmacogenetic information in Food and Drug Administration drug labeling and the table of pharmacogenetic associations. *Ann Pharmacother.* 2021;55:1185–1194. [PubMed: 33384014]

SELF-ASSESSMENT QUESTIONS

1. Newborn infants born prior to which of the following gestational ages are considered premature infants?
   A. 37 weeks
   B. 39 weeks
   C. 40 weeks
   D. 42 weeks
2. Kernicterus associated with sulfonamide in infants develops because of:
   A. Displacement of albumin by bilirubin
   B. Displacement of bilirubin from albumin by a sulfonamide
   C. Decreased metabolism of bilirubin
   D. Increased concentration of albumin
3. Compared with older patients, premature infants may have:
   A. Increased absorption of oral doses of weak acids such as phenobarbital
   B. Decreased absorption of intramuscular doses of all drugs
   C. Increased percutaneous absorption of drugs
   D. Rectal route should never be used in infants
4. Based on extracellular fluid (ECF) volume, which of the following populations is expected to have the largest apparent volume of distribution per kilogram of body weight for a drug largely distributed in ECF?
   A. Premature infants
   B. Children
   C. Adolescents
   D. Adults

5. Premature infants may need higher plasma concentrations of morphine for pain control than older patients because they have:

   A. Decreased metabolism to the more active metabolite

   B. Lower sensitivity to pain

   C. Increased urinary excretion of morphine

   D. Decreased absorption of morphine

6. Which of the following age groups generally requires the highest daily dose of theophylline per kilogram of body weight?

   A. 1-month-old infant

   B. 6-month-old infant

   C. 5-year-old child

   D. 15-year-old adolescent

7. Which of the following statements is true about adverse effects of drugs in pediatric patients?

   A. Tetracyclines are indicated for patients younger than 8 years of age.

   B. Benzyl alcohol is safe in premature infants.

   C. Promethazine is safe for use in infants.

   D. Aminoglycosides can be used safely in children at recommended doses with monitoring.

8. The FDA does not recommend the use of OTC cough and cold products in children younger than:

   A. 1 year

   B. 2 years

   C. 3 years

   D. 4 years

9. Ciprofloxacin has been approved by the FDA for use in children with:

   A. Community acquired Pneumonia

   B. Acute otitis media

   C. Complicated urinary tract infection

   D. Uncomplicated lower urinary tract infection

10. Knowledge of pharmacogenomics can be used to determine:

    A. Biomarker defined drug indication

    B. Polymorphic drug metabolism

    C. Susceptibility to adverse drug reactions

    D. All of the above

11. The daily dosage requirement of aminoglycosides in children with cystic fibrosis (CF) versus in those without CF is often:

    A. Increased

    B. Decreased

    C. Similar

    D. Unknown

12. The CDC and the American Academy of Pediatrics have categorized obese children as having a BMI percentile of:

    A. ≥99th

    B. ≥85th

    C. ≥95th

    D. None of the above

13. Chemotherapy dosing in pediatric obese patients should be based on BSA calculated by using:

    A. Lean body weight

    B. Actual body weight

    C. Ideal body weight

    D. Ideal body weight minus extracellular water weight

14. What percentage of adolescents with asthma may experience a problem with medication adherence?

    A. 10%

    B. 30%

    C. 60%

    D. 90%

15. Which of the following risk-reduction strategies may prevent and reduce medication errors to pediatric patients?

    A. Ordering standardized doses

    B. Dispensing pharmacy-prepared/ready-to-administer doses

    C. Implementing computerized physician order-entry system with dose range checking

    D. All the above strategies are correct

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** Infants born before 37 weeks of gestational age are considered premature because of underdeveloped organ systems including lungs, liver and brain. Those born at or above 37 weeks of gestational age are unlikely to experience health problems due to underdevelopment.

2. **B.** Sulfonamide can displace bilirubin bound to albumin in the plasma in infants. The increased amount of unbound bilirubin can cross the blood brain barrier and lead to kernicterus characterized by encephalopathy.

3. **C.** Absorption of orally administered a weak acid may be decreased due to higher gastric pH. Absorption of drugs after intramuscular administration is difficult to predict. Percutaneous absorption is increased due to underdeveloped epidermal barrier. Rectal route has been used for administration of certain drugs.

4. **A.** The extracellular fluid volume (ECF) per kilogram of body weight is highest in premature infants compared to older patients. Thus, the apparent volume of distribution per kilogram of drugs largely distributed in ECF is largest in the premature infants versus full-term infants, children, adolescents and adults.

5. **A.** Premature infants may not be able to metabolize morphine to its more active metabolite 6-glucuronide due to underdeveloped liver function. This may explain the need for higher dose of morphine to achieve the desired effect.

6. **C.** The clearance of theophylline per kilogram of body weight is highest in children of age 1 to 9 years in comparison to infants and adolescents. Thus, a 5-year old would require a higher dose of theophylline compared to an infant or an adolescent.

7. **D.** Tetracyclines are not indicated in children younger than 8 years due to adverse effects including dental staining and defects in enamelization and bone growth. Benzyl alcohol is contraindicated in premature infants due to severe toxicities including metabolic acidosis, neurologic adverse effects, and death. Promethazine has been associated with respiratory depression in infants. Aminoglycosides have been used safely at recommended doses with appropriate monitoring of serum concentration and kidney function.

8. **B.** Cough and cold products have been associated serious toxicities with overdoses in young children. Further, their efficacy has been unproven. Thus, the FDA does not recommend the use of these medications for children younger than 2 years.

9. **C.** Ciprofloxacin is approved by the FDA for complicated urinary tract infections because the benefits may exceed risks of adverse effects. There are many safer and effective alternative antibiotics for uncomplicated urinary tract infections. Ciprofloxacin would not adequately cover the pathogens causing community acquired pneumonia and acute otitis media.

10. **D.** Pharmacogenomic studies can be instrumental in individualizing the prescribing and the use of a drug and dosage regimen for a specific patient affected by an illness. The data can also be used for prevention or management of adverse drug reactions.

11. **A.** The clearance of aminoglycosides is markedly increased in children with cystic fibrosis (CF) in comparison with those without CF. Thus, patients with CF would require a higher daily dose of an aminoglycoside than those without CF.

12. **C.** The CDC and the American Academy of Pediatrics have defined obesity as the BMI percentile of 95th or greater. Studies have linked obesity with an increased risk of metabolic complications and development of comorbidities including hypertension and type 2 diabetes.

13. **B.** Studies have shown that chemotherapy dosing in obese patients should be based on BSA calculated by using actual body weight as in adults. Use of ideal or lean body weight may lead to underdosing and poor health outcomes.

14. **C.** As many as 60% of adolescents with asthma may experience difficulties with adherence to medications to control this condition.

15. **D.** Medication errors can be prevented or reduced by each of the three strategies mentioned above.