Introduction to Pediatrics[a]

Hanna Phan, Pharm.D., BCPS

The University of Arizona Colleges of Pharmacy and Medicine
Tucson, Arizona

Milap C. Nahata, Pharm.D., FCCP

The Ohio State University
Columbus, Ohio

[a]Reprinted with permission from Benavides S, Nahata M, eds. Pediatric Pharmacotherapy. Lenexa: American College of Clinical Pharmacy, 2013 ed. Lenexa, KS: American College of Clinical Pharmacy, 2013:3-17

Introduction to Pediatrics[a]

Hanna Phan, Pharm.D., BCPS

The University of Arizona Colleges of Pharmacy and Medicine
Tucson, Arizona

Milap C. Nahata, Pharm.D., FCCP

The Ohio State University
Columbus, Ohio

[a]Reprinted with permission from Benavides S, Nahata M, eds. Pediatric Pharmacotherapy. Lenexa: American College of Clinical Pharmacy, 2013 ed. Lenexa, KS: American College of Clinical Pharmacy, 2013:3-17

Learning Objectives

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

Abbreviations

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

I. THE ROLE OF A PEDIATRIC PHARMACIST

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

Pharmacists who care for pediatric patients should possess knowledge regarding disease states and drug therapy as well as the skills to apply this knowledge to practice. Pediatric practice includes a wide range of patient ages, with conditions varying from lower respiratory tract infection to trauma. Chronic disease states include lifelong or long-term diseases, such as type 1 diabetes mellitus, asthma, or congenital heart disease.

II. CLASSIFICATION OF PEDIATRIC PATIENTS

Pediatric patients are a specialized patient population. Their ages are expressed in days, weeks, months, or years. General classification is often age-dependent. Neonates are the patients from birth to younger than 28 days (4 weeks) of life when born full term, whereas infants are those 28 days to younger than 12 months. Children are often defined as 1–12 years of age. Adolescents can vary in definition, but they are most often recognized as age 13–17 years. Some government agencies combine adolescents with young adults who are up to 24 years of age (References 1, 10–12). Additional classifications are based on other factors such as birth weight and gestational age. For example, "low birth weight" is defined as having a birth weight between 1500 and less than 2500 g, and "premature" is defined as being born before 37 weeks of gestational age (Reference 10). An appreciation of the classification of pediatric patients is important in guiding medication selection because some medications are contraindicated for patients of certain ages. Medication dosing can also be affected by such classifications because dosing may depend on organ function (e.g., kidney or liver) development, which progresses with age. For example, neonates and infants lack the ability to metabolize alcohol by alcohol dehydrogenase, whereas adults have this ability. Thus, the use of elixir formulations should be avoided whenever possible in infants (Reference 13).

III. UNIQUENESS OF PEDIATRIC PHARMACOTHERAPY

Pediatric patients are unique because of their differences in regards to pharmacokinetics and pharmacodynamics (PK/PD), psychosocial influences on drug therapy selection, and treatment options from their adult counterparts. Developmental changes in PK/PD affect drug therapy selection and dosage requirements in the pediatric age continuum, from birth to 18 years. Pediatric clinicians must also consider factors that affect caregiver medication administration hesitance. These include cultural beliefs, socioeconomic status, and psychosocial differences

among age groups (e.g., child vs. adolescent). Pediatric patients also require special consideration when using specific drug formulations. For example, because children younger than 6 years are generally unable to swallow solid dosage forms, oral liquids are preferred for this younger age group.

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

IV. EPIDEMIOLOGY OF THE PEDIATRIC POPULATION

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

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

V. GROWTH AND DEVELOPMENT

Infants and children are often monitored for growth and development. Markers of physical growth include weight, length or height, head circumference, weight-for-length, and body mass index (BMI). These markers are age- and sex-dependent; therefore, the use of correct tools for measuring pertinent parameters on the basis of these factors is important for proper nutritional status and the physical growth assessment of pediatric patients. For children younger than 2 years, the World Health Organization (WHO) growth charts are recommended to assess these parameters (Figure 1). Since breastfeeding is the recommended standard for infants by the Centers for Disease Control and Prevention (CDC), the WHO growth charts reflect growth based on this feeding approach. The WHO growth patterns represent infants who were predominantly breastfed for at least 4 months duration and continue to breastfeed at 12 months of age. The CDC growth charts are recommended when assessing children 2 years and older (Figure 2) (Reference 22). Growth charts provide a graphic representation of a child's growth with respect to the general pediatric population among six countries including the United States. To use these charts, a patient's parameters (e.g., age and BMI) should be plotted on each axis, finding the cross-coordinate between the two parameters. This point should correlate with a percentile (e.g., 10th percentile) (Reference 22). Nutrition status is often assessed on the basis of growth percentiles (e.g., BMI). Also noteworthy is the gradual development of organ (e.g., kidney and liver) function and drug distribution space (e.g., total body water) affecting the PK/PD of drugs administered to the patients.

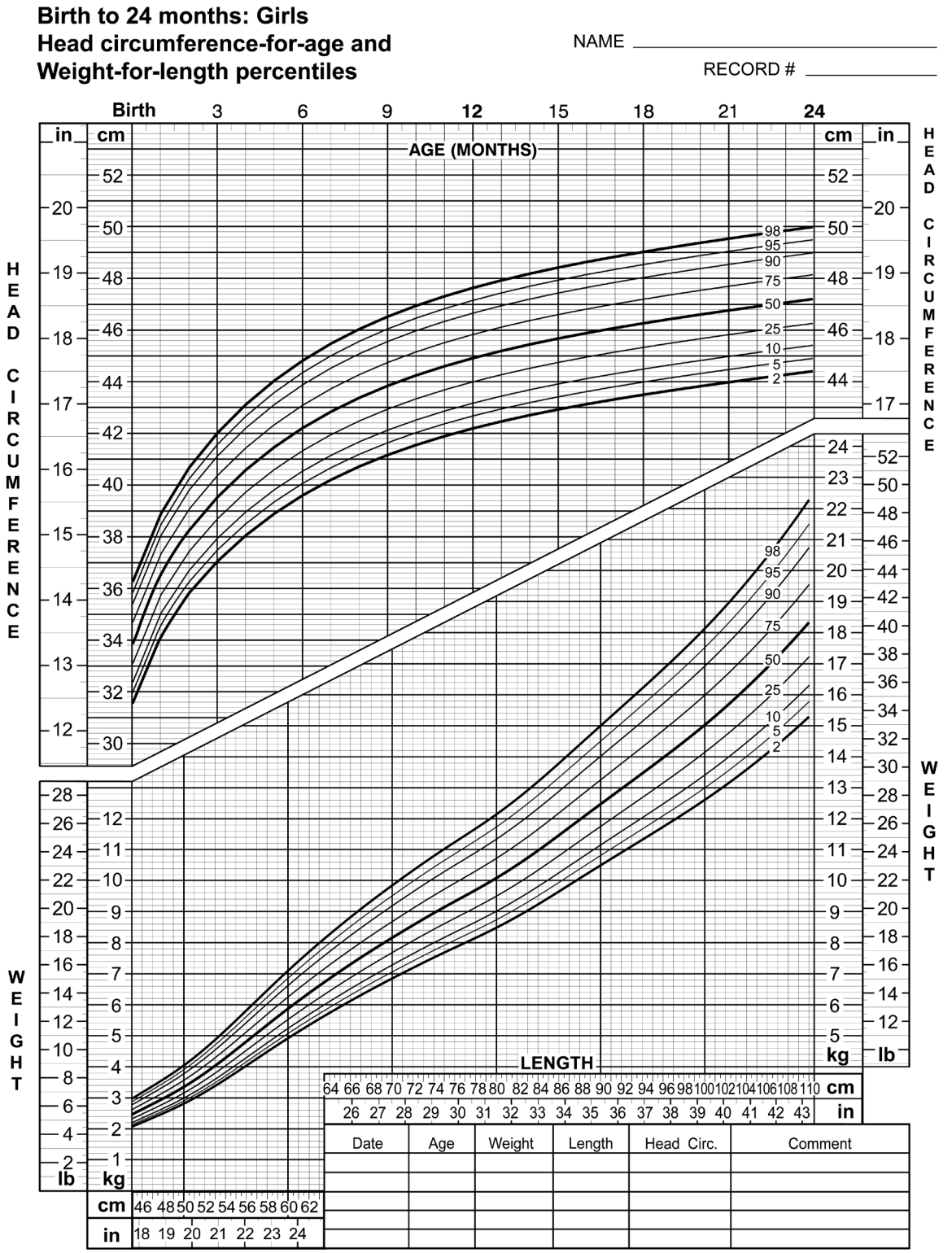

Figure 1. Example of WHO growth chart: girls (age 0–24 months), head circumference-for-age and weight-for-length percentiles (Reference 22).

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

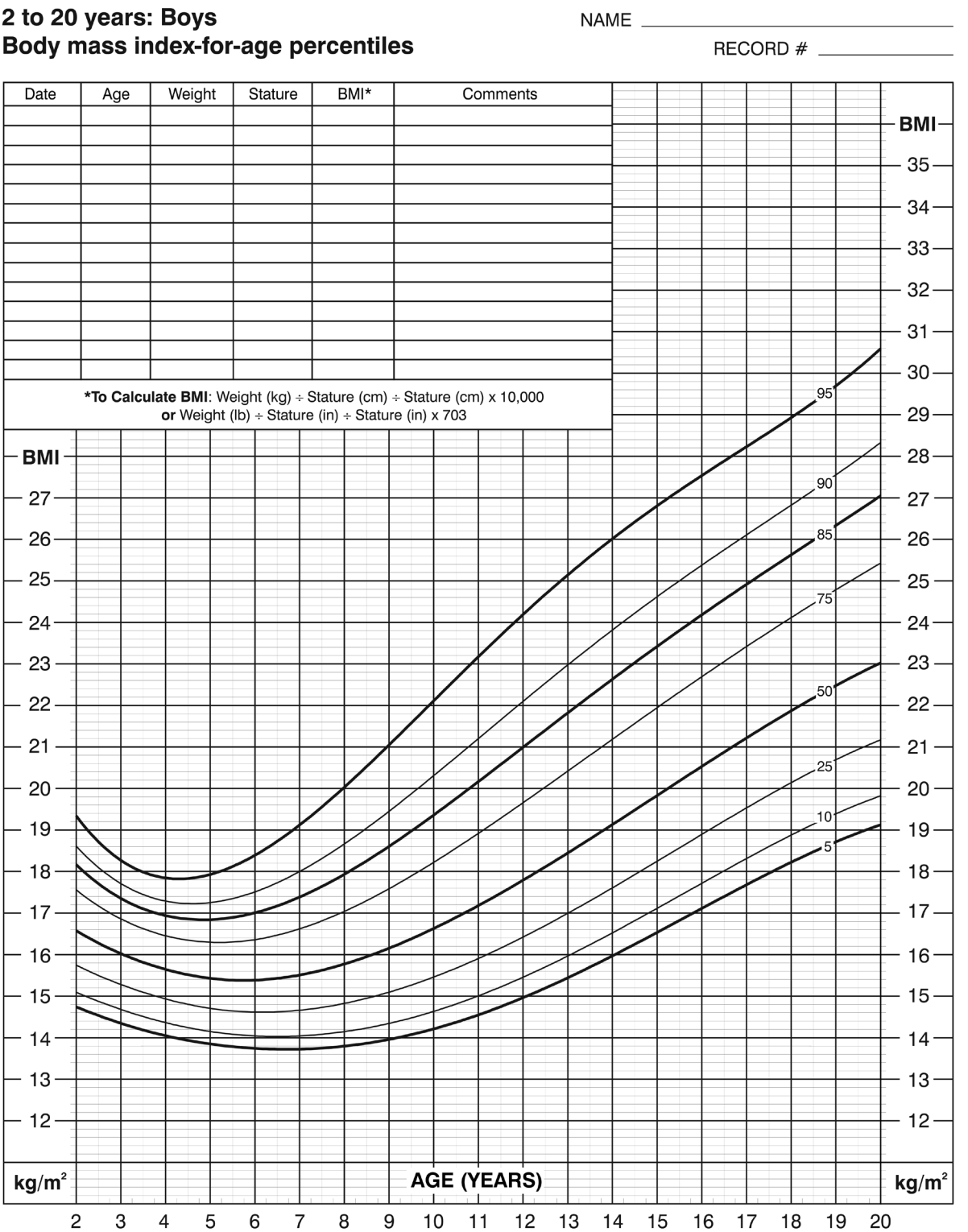

Figure 2. Example of CDC growth chart: boys (age 2–20 years), body mass index-for-age percentiles, 2000 (Reference 22).

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

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

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

VI. DIFFERENCES IN PEDIATRIC PATIENT DATA—VITAL SIGNS, LABORATORY VALUES, AND CALCULATIONS

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

A. Vital Signs

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

breaths/minute and, around adolescence, approaches adult values at 12–16 breaths/minute (Reference 28). The AAP guidelines provide blood pressure reference ranges for assessment on the basis of age, sex, and height for children 1 year or older. In general, systolic blood pressure at the 50th percentile can range from 80 to 98 mm Hg, 91 to 106 mm Hg, and 99 to 122 mm Hg, and diastolic pressure can range from 34 to 56 mm Hg, 53 to 63 mm Hg, and 59–70 mm Hg at age ranges 1–5, 6–11, and 12–17 years, respectively. For specific ranges based on height percentile, sex, and age, one should refer to the Report on Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents (Reference 29). Overall, heart and respiratory rates decrease with age, and blood pressure increases with age.

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

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

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

B. Laboratory Values

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

C. Calculations

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

VII. CHALLENGES OF MEDICATION ADHERENCE

Medication adherence, defined as the "extent to which patients take (or in the care of younger pediatric patients, are given) medications as prescribed," is a challenge for all patient populations; pediatric patients are no exception to this continued health care issue (Reference 50). Although chronic illnesses, such as asthma and diabetes mellitus, are often associated with a high potential for poor adherence, short antibiotic treatment courses for conditions such as acute otitis media are also worth investigating (Reference 50). Consequences of nonadherence include delayed or absent clinical improvement, worsening of illness, and unnecessary therapy modifications that can lead to adverse clinical outcomes. Medication adherence is often difficult to document in ambulatory care practice environments. Approaches to measuring medication adherence include self-report, clinician's impression, dose count (e.g., pills or inhaler counter), refill verification, and monitoring of serum drug concentrations when appropriate (References 51, 52). Devices such as electronic monitors have been used in research settings. However, these are not commonplace in clinic settings and are cost-prohibitive for routine use at this time (Reference 53). Nonadherence, often considered adhering to a prescribed therapy less than 80% of the time, is multifaceted in nature. Moreover, identifying approaches to improve adherence is challenging. Reasons for poor adherence include forgetting the time to administer doses, experiencing difficulty with caregiver's and/or patient's personal beliefs, encountering socioeconomic limitations, experiencing adverse drug effects, and having unpleasant or inconvenient medication formulation or schedules, as well as child psychological factors, such as peer acceptance among adolescents. In general, younger children (e.g., younger than 5 years) have greater medication adherence to the treatment of chronic illnesses such as asthma (Reference 52). This is because of caregiver responsibility and action in administering necessary medication in most cases. However, it should not be assumed that all caregivers adhere to prescribed treatment regimens. Caregiver education is imperative with every medication dispensed for a child.

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

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

Calculation	Equation
Body surface area (BSA)[a]	BSA (m^2) = sqrt [(height × weight) ÷ 3600]
Body mass index (BMI)[a]	BMI = weight ÷ height ÷ height × 10,000
Ideal body weight (IBW)[a]	IBW (kg) = [$(height)^2$ × 1.65] ÷ 1000
Creatinine clearance (CrCl)	Original Schwartz Equation CrCl (mL/minute/1.73m2) = [k × L] ÷ SCr k = proportionality constant L = length in centimeters SCr = serum creatinine in mg/dL

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

	Bedside Schwartz Equation (patients younger than 1 year) CrCl = [0.413 × height (in cm)]/SCr (in mg/dL)
Estimation of pediatric dosing when limited pediatric-dosing data are available	Approximate pediatric dose = adult dose × [BSA (in m2) ÷ 1.73m2]

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

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

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

Different approaches have been suggested to improve medication adherence. Behavioral and educational approaches have received the most emphasis in studies regarding chronic diseases such as pediatric asthma and diabetes mellitus (References 56, 57). Caregiver education regarding medications should be reinforced at several points of health care visits because it is important to enhance the caregiver's understanding of the importance

and benefit of completing treatment and the risk of adverse effects. Ease of administration, including palatable dosage forms and the need for less frequent dosing, can help caregivers keep to a treatment schedule. Poor palatability of medication, specifically liquid medications, can negatively affect medication adherence. Despite the lack of extensive research data, clinician and parental experiences have shown the importance of palatability as a target to improve adherence (Reference 52, 54). The use of a reward system and positive reinforcement may aid in decreasing resistance by young children during treatment periods. Empowering older children and adolescents positively with knowledge about their disease may improve self-management of drug therapy and medication adherence (Reference 55).

VIII. OFF-LABEL MEDICATION USE IN PEDIATRIC PATIENTS

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

Regulatory changes have been made to decrease the off-label use of drugs in the pediatric population. The Pediatric Rule, issued in 1994, permitted manufacturers to label drugs for pediatric use on the basis of extrapolated efficacy data and additional PK/PD data specific to the pediatric population when disease and therapy response were considered similar to those of their adult counterparts (Reference 58). Unfortunately, this resulted in only a few well-conducted studies regarding infants and children because of the difficulties involved in predicting dose-response from adult data. The FDA Modernization Act (FDAMA) followed in 1997, offering a financial incentive of 6 months' extended market exclusivity for performing pediatric studies (Reference 59). Because of the FDAMA, additional drugs were assigned pediatric labeling. However, efficacy data were still lacking. In 2002, an incentive-based Best Pharmaceuticals for Children Act (BPCA) was implemented, extending the FDAMA and offering a 6-month extension of patent exclusivity to encourage industry to conduct pediatric studies for branded products labeled only for adults (Reference 60). The Pediatric Research Equity Act (PREA) of 2003 also provided potential requirements for the pediatric assessment of drug applications submitted to the FDA for approval in adults. This assessment includes the potential use and evaluation of risk versus benefit in pediatric patients (Reference 58). The FDA pediatric decision tree, a process whereby agents are evaluated for pediatric study regarding PK/PD, efficacy, and safety, is depicted in Figure 3 (Reference 61). For rare diseases with an occurrence of 200,000 people or less in the United States, such as inborn errors of metabolism, the Orphan Drug Act provides support in the development of needed treatment (Reference 62).

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

Because of limited pediatric-specific guidelines for much of drug therapy, use of primary literature is crucial in providing evidence-based care to infants, children, and adolescents. Although randomized, placebo-controlled

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

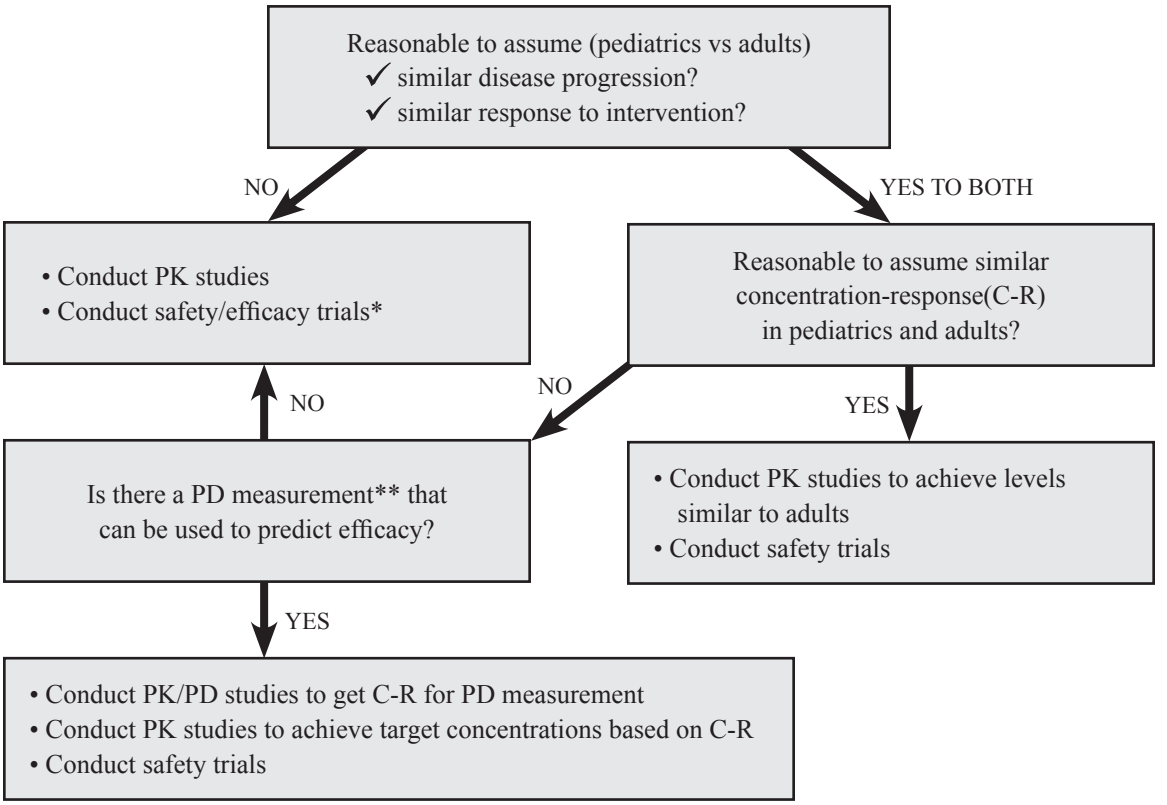

Figure 3. The FDA pediatric decision tree (Reference 61).
C-R = concentration response; PD = pharmacodynamic; PK = pharmacokinetic.
Reprinted from: U.S. Food and Drug Administration: Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications. Available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInforma-tion/Guidances/ucm072109.pdf. Accessed May 9, 2012.

A dilemma with newer adult drug therapy options is that there is no exact, recommended approach to dosing such agents in pediatric patients, especially because the agents have no pediatric indication. Although adult dosing often involves a standard dose for of the population regardless of age and weight (e.g., omeprazole 20 mg orally daily), pediatric dosing is often weight-dependent (e.g., omeprazole 1 mg/kg orally daily). Pediatric dosages may also be based on age (e.g., neonate vs. child). Rounding of doses is a dilemma not often seen in the care of adults. In pediatric patients, doses of wide-therapeutic index medications (e.g., antibiotics) can be rounded for ease of measurement. Some institutions round doses by 10% to 20%, depending on the risks associated with a given medication.

In the past, approaches to dosing included Fried's Rule, Clark's Rule, or Young's Rule to estimate dosing when pediatric-specific data were not available. However, these equations differentiated a child from an adult by one factor of difference such as age in months or years or weight in pounds. This approach oversimplifies the known complex differences between the pediatric and adult populations. As a result, these approaches can

over- or underestimate dosing in pediatric patients. Thus, these methods are no longer recommended for estimating off-label dosing in pediatric patients. If there is no alternative therapy—or if there are limited or no pediatric data for dosing but evidence to support the safety of the drug in pediatric patients—some clinicians may elect to dose on the basis of the body surface area ratio if the child is of normal height and weight for age (Table 1) (Reference 64). However, of note, this method is not a well-studied approach to off-label medication dosing, and caution should be used when considering this option. A potential exists for unaccounted differences in PK/PD between pediatric and adult patients when using this dose-estimating approach, resulting in differences in efficacy and safety. Thus, clinical judgment should be applied when considering off-label medication use and dosing in instances of limited pediatric data.

IX. MEDICATION SAFETY

Medication errors are preventable events that result from human or system flaws (Reference 9). Pediatric patients are at increased risk of medication errors, with an error rate of 15% of pediatric medication orders compared with 5% of adult medication orders (Reference 9). Prescribing and transcription errors account for many of the medication errors in U.S. neonatal and pediatric intensive care units at 50% of all errors. Because pediatric doses are often calculated (e.g., milligram per kilogram), the risk of calculation error is high. Accuracy and consistency in the units of measurement used are important in preventing calculation and prescribing errors. Decimal errors, such as trailing zeros (e.g., 5.0 mg) and missing leading zeros (e.g., .5 mg), also result in 10-fold or greater errors. Calculation inaccuracies can lead not only to prescribed dose error, but they can also cause error when medications are compounded into intravenous solutions or oral suspensions. One should also be cautious of potential dispensing errors when the incorrect strength of a medication is selected.

Calculation errors can be reduced through computer physician order entry, which can provide automated medication-dosing calculators and mandatory prescription order fields (Reference 65). The use of an alert-based decision support system can potentially prevent several errors; however, it also has the potential to cause "alert fatigue" because of too many unnecessary alerts, which can lead a clinician to bypass warnings for incorrect medication orders. Barcode technology has also helped reduce the incorrect selection and administration of medications (Reference 66). Medication administration error rates have also decreased with the use of technologies such as smart pumps for parenteral medications in daily care (Reference 67). Despite technological advances, however, a potential for human or system error remains during the process of preparing, dispensing, and administering medications. Thus, medication error prevention is a multifaceted task involving the active participation of the health care team as well as the patient and caregiver. Communication between all parties and continued efforts to improve medication use practice are essential in the provision of safe patient care.

X. FUNDAMENTALS OF PEDIATRIC PATIENT CARE

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

A. Infants and Young Children
   1. Educate the caregiver about the purpose, effectiveness, and potential adverse effects of the medication.
   2. For children younger than 3 years, review birth history and history of illness, including hospitalizations; review medical record for assessment of cognitive and motor skills development.
   3. Note body weight, height, and head circumference (for infants), and assess growth percentiles (e.g., by using the WHO or CDC growth chart).
   4. For infants, evaluate weight-based dosing regularly, especially for medications used in chronic illnesses that require dose adjustments with growth (e.g., weight gain).

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

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

C. Overall Drug Therapy Assessment

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

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

D. Patient and Caregiver Education

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

1. Reason(s) for medication use
2. Dose measurement (with appropriate device)
3. Medication storage
4. Potential adverse drug effects
5. Therapy duration
6. If therapy is chronic and requires laboratory monitoring, discuss what these tests are, why they are used for monitoring efficacy or safety, and how frequently they would be done.
7. Expected therapy outcomes

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

XI. THE PRESENT AND FUTURE OF PEDIATRIC PHARMACY PRACTICE

Pediatric patients are seen in all health care settings, including community pharmacies, clinics, physician offices, community hospitals, and large academic, tertiary institutions. A fundamental understanding of the needs of this special population is essential for the provision of patient care by pharmacists. Although pharmacists in the community setting often lack specialty training in pediatric practice, all pharmacy practitioners should have an appreciation of general concepts in pediatrics, such as approaches to dosing (e.g., milligram per kilogram), unique pharmacokinetics, and drug administration needs, as well as the ability to identify potential drug-related problems (e.g., contraindicated medications for certain age groups). Pediatric pharmacy practice is a growing specialty area of pharmacy practice, serving future generations of patients with a mission focused on patient advocacy and provision of safe and effective drug therapy through professional responsibility, education, and research. This area of practice will continue to grow with its expansions in the professional pharmacy school curriculum and continued education training in pediatric postgraduate residencies and fellowships. Practice opportunities in pediatric pharmacy have expanded beyond the pharmacy counter, with an increasing number of pharmacists working as part of interdisciplinary teams in the care of infants, children, and adolescents, from intensive care units to specialist clinics such as cystic fibrosis centers nationwide. Opportunities exist to advance pediatric practice for present and future generations of pharmacists, including expanding the role of pharmacists in areas such as pediatric immunizations, chronic care management, and continuity of care between inpatient

and outpatient care. Pharmacists must also initiate and participate in pediatric pharmacotherapy research to advance health care and the profession. Examples of pharmacist- driven innovations include increasing the understanding of approaches to drug therapy management, discovering new therapeutic approaches, and developing behavioral interventions to optimize medication adherence. This partnership of advanced practice and scholarship is what the pharmacy profession must promote to make unique contributions to the body of knowledge in pediatrics and provide quality patient care.

XII. ADDITIONAL GENERAL PEDIATRIC RESOURCES

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

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

Web sites

American Academy of Pediatrics (AAP) – www.aap.org
Pediatric Pharmacy Advocacy Group (PPAG) – www.ppag.org

References

*Kliegman RM, Stanton BMD, St. Geme J, Schor N. Berhman RE. Nelson Textbook of Pediatrics, 19th ed.Philadelphia: Saunders, 2011.
*Taketomo CK, Hodding JH, Kraus DM. Pediatric & Neonatal Dosage Handbook, 18th ed. Hudson, OH: Lexi-Comp, 2011.
*Arcara K, Tschudy M. The Harriet Lane Handbook, 19th ed. Philadelphia: Elsevier Mosby, 2011.
*Nahata MC, Pai VB. Pediatric Drug Formulations, 6th ed. Cincinnati: Harvey Whitney, 2011.
Phelps SJ, Hak EB, Crill CM. Pediatric Injectable Drugs: The Teddy Bear Book, 9th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2010.
*Buck ML, Hendrick AE. Pediatric Medication Education Text, 5th ed. Lenexa, KS: American College of Clinical Pharmacy, 2009.
**Available in print and electronically.*

REFERENCES

1. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology-drug disposition, action, therapy in infants and children. N Engl J Med 2003;349:1157–67.
2. Pediatric Pharmacy Administration Group Committee on Pediatric Pharmacy Practice. Pediatric pharmacy practice guidelines. Am J Hosp Pharm 1991;48:2475–7.
3. American Society of Hospital Pharmacists. ASHP guidelines for providing pediatric pharmaceutical services in organized health care systems. Am J Hosp Pharm 1994;51:1690–2.
4. Educational Outcomes, Goals, and Objectives for Postgraduate Year Two (PGY2) Pharmacy Residencies in Pediatrics. American Society of Health-System Pharmacists and Pediatric Pharmacy Advocacy Group. Available at www.ashp.org/searchresults.aspx?q=educational outcomes. Accessed May 10, 2012.
5. Pediatric Pharmacy Advocacy Group. Comments on ASHP Guidelines on Providing Pediatric Pharmaceutical Services. Available at www.ppag.org/ attachments/articles/6/ASHP_response.pdf. Accessed May 10, 2012.
6. Kennedy MJ, Phan H, Benavides S, Potts A, Sorensen S. Pediatric Pharmacy Advocacy Group, Position Statement. The Role of the Pediatric Pharmacist in Personalized Medicine and Clinical Pharmacogenomics for Children. Available at www.ppag.org/pharmacogenomics-position/. Accessed May 10, 2012.
7. Aucoin RG, Buck ML, Dupuis LL, Dominguez KD, Smith KP. Pediatric pharmacotherapeutic education: current status and recommendations to fill the growing need. Pharmacotherapy 2005;25:1277–82.
8. Phan H, Pai VB, Nahata MC. Pediatrics. In: Chisholm-Burns MA, Schwinghammer TL, Wells BG, Malone P, Kolesar J, DiPiro J, eds. Pharmacotherapy: Principles and Practice, 2nd ed. New York: McGraw-Hill, 2010:23–33.
9. American Academy of Pediatrics Committee on Drugs; American Academy of Pediatrics Committee on Hospital Care. Prevention of medication errors in the pediatric inpatient setting. Pediatrics 2003;112:431–6.
10. American Academy of Pediatrics, Committee on Fetus and Newborn. Age terminology during the perinatal period. Pediatrics 2004;114:1362–4.
11. Guidance for Industry, E11 Clinical Investigation of Medicinal Products in the Pediatric Population. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), and Center for Biologics and Evaluation and Research (CBER). December 2000. Available at www.fda.gov/downloads/ RegulatoryInformation/Guidances/ucm129477.pdf. Accessed May 10, 2012.
12. Mulye TP, Park MJ, Nelson CD, Adams SH, Irwin CE Jr, Brindis CD. Trends in adolescent and young adult health in the United States. J Adolesc Health 2009;45:8–24.
13. Strolin Benedetti M, Baltes EL. Drug metabolism and disposition in children. Fundam Clin Pharmacol 2003;17:281–99.
14. Bazzano AT, Mangione-Smith R, Schonlau M, Suttorp MJ, Brook RH. Off-label prescribing to children in the United States outpatient setting. Acad Pediatr 2009;9:81–8.
15. Shah SS, Hall M, Goodman DM, Feuer P, Sharma V, Fargason C Jr, et al. Off-label drug use in hospitalized children. Arch Pediatr Adolesc Med 2007;161:282–90.
16. U.S. Census Bureau. National Population Estimates: Characteristics. Available at www.census.gov/popest/ data/national/asrh/2011/index.html. Accessed May 10, 2012.
17. Statistics Canada. Canadian Statistics. Available at www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo10a-eng.htm. Accessed May 10, 2012. 16 ? Introduction
18. Bloom B, Cohen RA, Freeman G. Summary health statistics for U.S. children: National Health Interview Survey, 2009. National Center for Health Statistics. Vital Health Stat 10. 2010; Dec;(247):1–82.

19. Hing E, Hall MJ, Ashman JJ, Xu J. National Hospital Ambulatory Medical Care Survey: 2007 Outpatient Department Summary. National Health Statistics Reports; No. 28. Hyattsville, MD: National Center for Health Statistics, 2010.
20. Hall MJ, DeFrances CJ, Williams SN, Golosinskiy A, Schwartzman A. National Hospital Discharge Survey: 2007 Summary. National Health Statistics Reports; No. 29. Hyattsville, MD: National Center for Health Statistics, 2010.
21. Niska RW, Bhuiya FA, Xu J. National Hospital Ambulatory Medical Care Survey: 2007 Emergency Department Summary. National Health Statistics Reports; No. 26. Hyattsville, MD: National Center for Health Statistics. 2010. Available at www.cdc.gov/nchs/data/nhsr/nhsr026.pdf. Accessed May 10, 2012.
22. Centers for Disease Control and World Health Organization Growth Charts. Available at www.cdc. gov/growthcharts. Accessed May 10, 2012.
23. Feigelman S. The first year. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics. Philadelphia: Saunders Elsevier, 2007:43–7.
24. Feigelman S. The second year. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, eds. Nelson Textbook of Pediatrics. Philadelphia: Saunders Elsevier, 2007:48–53.
25. Council on Children with Disabilities; Section on Developmental Behavioral Pediatrics; Bright Futures Steering Committee; Medical Home Initiatives for Children With Special Needs Project Advisory Committee. Identifying infants and young children with developmental disorders in the medical home: an algorithm for developmental surveillance and screening. Pediatrics 2006;118:405–20.
26. Piaget J, Inhelder B. The Psychology of the Child. New York: Basic Books, 1969.
27. Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011;377:1011–8.
28. American Heart Association. Pediatric Advanced Life Support Provider Manual. Dallas: American Heart Association, 2006.
29. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004;114(2 suppl 4th report):555–76.
30. American Academy of Pediatrics. (2007). Parenting Corner Q&A: What's the Best Way to Take a Child's Temperature? Available at www.healthychildren.org/English/health-issues/conditions/fever/pages/How-to- Take-a-Childs-Temperature.aspx. Accessed May 10, 2012.
31. Doezema D, Lunt M, Tandberg D. Cerumen occlusion lowers infrared tympanic membrane temperature measurement. Acad Emerg Med 1995;2:17–9.
32. Greenes DS, Fleisher GR. Accuracy of a noninvasive temporal artery thermometer for use in infants. Arch Pediatr Adolesc Med 2001;155:376–81.
33. Sullivan JE, Farrar HC. Section on Clinical Pharmacology and Therapeutics and Committee on Drugs. Clinical report – fever and antipyretic use in children. Pediatrics 2011;127:580–7.
34. Baraff LJ, Bass JW, Fleisher GR, Klein JO, McCracken GH Jr, Powell KR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without source. Agency for Health Care Policy and Research. Ann Emerg Med 1993;22:1198–210.
35. Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Netw 1993;12:59–66.
36. Merkel SI, Voepel-Lewis T, Shayevitz JR, Malviya S. The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatr Nurs 1997;3:293–7.
37. Hockenberry MJ, Wilson D, Winkelstein ML. Wong's Essentials of Pediatric Nursing, 7th ed. St. Louis: Mosby, 2005:1259.
38. Arcara K, Tschudy M. The Harriet Lane Handbook, 19th ed. Philadelphia: Elsevier Mosby, 2011.
39. Taketomo CK, Hodding JH, Kraus DM. Pediatric & Neonatal Dosage Handbook, 18th ed. Hudson, OH: Lexi-Comp, 2011.
40. Mosteller RD. Simplified calculation of body surface area. N Engl J Med 1987;317:1098.

41. Mei Z, Grummer-Strawn LM, Pietrobelli A, Goulding A, Goran MI, Dietz WH. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. Am J Clin Nutr 2002;75:978–85.
42. Traub SL, Kichen L. Estimating ideal body mass in children. Am J Hosp Pharm 1983;40:107–10.
43. 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;34:571–90.
44. Staples A, LeBlond R, Watkins S, Wong C, Brandt J. Validation of the revised Schwartz estimating equation in a predominantly non-CKD population. Pediatr Nephrol 2010;25:2321-6.
45. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
46. Jeliffe RW. Creatinine clearance: bedside estimate. Ann Intern Med 1973;79:604–5.
47. Seikaly MG, Browne R, Bajaj G, Arant BS Jr. Limitations to body length/serum creatinine ratio as an estimate of glomerular filtration in children. Pediatr Nephrol 1996;10:709–11. Introduction to Pediatrics ? Phan and Nahata ? 17
48. Filler G, Lepage N. Should the Schwartz formula for estimation of GFR be replaced by cystatin C formula? Pediatr Nephrol 2003;18:981–5.
49. Schwartz GJ, Muñoz A, Schneider MF, Mak RH, Kaskel F, Warady BA, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol 2009;20:629–37.
50. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487–97.
51. Matsui DM. Drug compliance in pediatrics clinical and research issues. Pediatr Clin North Am 1997;44:1–14.
52. Matsui D. Current issues in pediatric medication adherence. Pediatr Drugs 2007;9:283–8.
53. De Bleser L, De Geest S, Vincke B, Ruppar T, Vanhaecke J, Dobbels F. How to test electronic adherence monitoring devices for use in daily life: a conceptual framework. Comput Inform Nurs 2011;29:489–95.
54. Winnick S, Lucas DO, Hartman AL, Toll D. How do you improve compliance? Pediatrics 2005;115:e718–24.
55. Ou HT, Feldman SR, Balkrishnan R. Understanding and improving treatment adherence in pediatric patients. Semin Cutan Med Surg 2010;29:137–40.
56. McQuaid EL, Kopel SJ, Klein RB, Fritz GK. Medication adherence in pediatric asthma: reasoning, responsibility, and behavior. J Pediatr Psychol 2003;28:323–33.
57. Bond GG, Aiken LS, Somerville SC. The health belief model and adolescents with insulin-dependent diabetes mellitus. Health Psychol 1992;11:190–8.
58. Pediatric Research Equity Act. Public Law 108–155. Available at www.fda.gov/downloads/ Drugs/DevelopmentApprovalProcess/ DevelopmentResources/ UCM077853.pdf. Accessed May 10, 2012.
59. Food and Drug Administration Modernization Act of 1997 (FDAMA). Available at www.fda.gov/oc/ fdama/ default.htm. Enacted 21 November 1997. Accessed May 10, 2012.
60. Best Pharmaceuticals for Children Act. Public Law 107–109. Available at www.fda.gov/ downloads/ Drugs/DevelopmentApprovalProcess/ DevelopmentResources/UCM049874.pdf. Accessed May 10, 2012.
61. U.S. Food and Drug Administration: Guidance for Industry: Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications. Available at www.fda.gov/downloads/ Drugs/GuidanceComplianceRegulatoryInformation/ Guidances/ ucm072109.pdf. Accessed May 10, 2012.
62. The Orphan Drug Act. Available at www. fda.gov/ RegulatoryInformation/Legislation/ FederalFoodDrugandCosmeticActFDCAct/ SignificantAmendmentstotheFDCAct/ OrphanDrugAct/default.htm. Accessed May 9, 2012.
63. National Asthma Education and Prevention Program National Heart, Lung and Blood Institute. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Washington, DC: U.S. Department of Health and Human Services, 2007.
64. Shirkey HC. Drug dosage for infants and children. JAMA 1965;193:443–6.

65. Potts AL, Barr FE, Gregory DF, Wright L, Patel NR. Computerized physician order entry and medication errors in a pediatric critical care unit. Pediatrics 2004;113(1 pt 1):59–63.
66. Poon EG, Keohane CA, Yoon CS, Ditmore M, Bane A, Levtzion-Korach O, et al. Effect of bar-code technology on the safety of medication administration. N Engl J Med 2010;362:1698–707.
67. Larsen GY, Parker HB, Cash J, O'Connell M, Grant MC. Standard drug concentrations and smart-pump technology reduce continuous-medication-infusion errors in pediatric patients. Pediatrics 2005;116:e21–5.
68. American Academy of Pediatrics (AAP). Available at www.aap.org/. Accessed May 9, 2012.
69. Pediatric Pharmacy Advocacy Group (PPAG). Available at www.ppag.org/. Accessed May 9, 2012.
70. Nahata MC, Pai VB. Pediatric Drug Formulations, 6th ed. Cincinnati: Harvey Whitney, 2011.
71. Kliegman RM, Stanton BMD, St. Geme J, Schor N, Berhman RE. Nelson Textbook of Pediatrics, 19th ed. Philadelphia: Saunders, 2011.
72. Phelps SJ, Hak EB, Crill CM. Pediatric Injectable Drugs: The Teddy Bear Book, 9th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2010.
73. Buck ML, Hendrick AE. Pediatric Medication Education Text, 5th ed. Lenexa, KS: American College of Clinical Pharmacy, 2009.