

## Pharmacotherapeutics

### Factors Affecting Pharmacokinetics

Many nonpediatric providers think of children as small adults, but this is not the case. As children grow, their bodies undergo changes in absorption, distribution, metabolism, and excretion; all of which affect the pharmacokinetics of drugs in this population. Many of the drugs and dosages used in infants and children are not specifically approved by the US Food and Drug Administration (FDA) for those indications of patient populations. Some of the drugs and dosages recommended in this text are not FDA approved, but are widely accepted as appropriate

- Absorption
  - Influenced by:
    - ▶ Age
    - ▶ Physiological condition
    - ▶ Drug dosage, form, and physical properties
    - ▶ Interactions with concurrent medications and foods
  - Absorption of oral drugs
    - ▶ Absorption mostly takes place in the small intestine, where pH range is 4–8
    - ▶ The pH of neonatal gastric fluid is neutral to slightly acidic, but becomes more acidic as the infant matures. It usually reaches adult values by 2 years of age, but may take as long as 6 years of age; this higher gastric pH affects the absorption of some drugs (eg, phenytoin, phenobarbital, ampicillin, nafcillin, and penicillin G)
    - ▶ Neonates have erratic, prolonged gastric emptying times and intestinal transit times, which leads to increased absorption; gastric emptying time reaches adult values by 6–8 months of age
    - ▶ Older children have faster gastric emptying and transit time, which leads to decreased absorption
    - ▶ During the first few months of life, neonates have

- immature biliary function that results in a decreased amount of bile salts and decreased absorption of lipid-soluble drugs (eg, vitamin E)
- ▶ Concurrent administration of infant formulas or milk products temporarily increases pH and may impede absorption of acidic drugs
- ▶ Critical illness often shunts blood from the gut to the heart and brain, effectively decreasing the gut's ability to absorb medication
- ▶ Neonates, infants, and young children should receive oral medications on an empty stomach unless the pharmacokinetics for the specific medication will be affected by the presence of food and change in pH
- Absorption of parenteral drugs
  - ▶ Because neonates and young infants have small skeletal muscle mass and variable blood flow, the absorption of drugs administered via the intramuscular (IM) and subcutaneous (SQ) routes may be unpredictable
  - ▶ Properties of some medications influence IM absorption (eg, phenobarbital [rapid], diazepam [slow])
- Absorption of topical drugs
  - ▶ Neonates and infants have enhanced absorption of topical drugs due to the relative thinness and the high water concentration of their skin
  - ▶ Neonates and infants possess a high proportion of body surface area (BSA) to total body mass, which can lead to systemic, toxic, and/or adverse reactions to topical agents (eg, isopropyl alcohol, steroid ointments, and hexachlorophene soaps)
- Distribution
  - Developmental changes in body composition affect drug distribution
    - ▶ Term neonate: body fluid equals 55%–70% of total body weight
    - ▶ Premature infant: body fluid equals up to 85% of total body weight
    - ▶ Adult: body fluid equals 50%–55% of total body weight
    - ▶ During the first 12 months after birth, total body fluid decreases dramatically, then gradually decreases to

- adult proportions by 12 years of age
- ▶ Extracellular fluid is 40% of a neonate's weight (as opposed to 20% of adult's weight)
- Solubility in lipids versus water affects distribution of drugs and dosages
  - ▶ A higher proportion of fluid to body weight greatly enhances the distribution of water-soluble drugs
  - ▶ The low ratio of fat to muscle in children limits the distribution of fat-soluble drugs
- Plasma protein binding affects distribution; only free (unbound) drug can exert a pharmacological effect
  - ▶ Children < 3 months old have significantly less albumin and  $\alpha_1$ -acid glycoprotein than adults; drugs that bind primarily to these proteins must be administered in reduced doses
  - ▶ Drug binding to plasma protein reaches adult levels by approximately 12 months of age
  - ▶ The affinity of plasma proteins to bind with drugs is reduced in the neonate
  - ▶ Bilirubin and free fatty acids compete with drugs for binding sites on plasma proteins and further reduce the protein-binding abilities of drugs in neonates; sulfonamides, salicylates, penicillins, and furosemide displace bilirubin from plasma proteins
- Immaturity of the blood–brain barrier in neonates results in greater drug penetration of cerebrospinal fluid (eg, aminoglycosides)
- Metabolism
  - Most drugs are metabolized in the liver
    - ▶ Neonates have a large liver (40% of body mass vs 2% in adults); therefore, they have a relatively larger surface area for metabolism
    - ▶ A neonate's immature liver and enzyme system may impede metabolism
      - ▷ Some enzymes reach adult levels at a few months of age, while others may take years
      - ▷ The ability of a child to metabolize many drugs may not be developed fully until 12–15 months of age
    - ▶ Older infants and children metabolize some drugs more

- rapidly than adults (eg, carbamazepine, quinidine, phenytoin)
- Enzymatic functions mature at different ages
  - ▶ Glucuronidation (mechanism to assist the liver in eliminating toxins) is not sufficiently developed until 1 month of age
  - ▶ Standard pediatric dosages of some drugs may produce adverse or toxic reactions in neonates (eg, chloramphenicol)
  - ▶ Older infants and children can metabolize some drugs more rapidly than adults and may require larger doses to achieve a therapeutic effect
  - ▶ Intrauterine exposure to drugs may induce early development of hepatic enzymes, which will result in increased capacity to metabolize drugs
- Concurrent drug use can produce interactions that may stimulate or reduce liver enzyme activity (eg, phenobarbital can increase metabolism of phenytoin, requiring an increased dose of phenytoin)
- Excretion
  - Most drugs and metabolites are excreted in the urine
  - Renal excretion involves glomerular filtration and tubular secretion, the former being more developed at birth
  - Glomerular filtration rate reaches adult levels by 12 months of age in most full-term infants; premature infants will take longer to reach adult levels
  - Renal tubular secretion mechanisms become fully functional after glomerular filtration rate has reached adult levels
  - Maturity of the renal system and presence of renal disease can affect drug dosage requirements; renal function is much more developed in full-term neonates than in premature infants
  - Inadequate renal excretion results in drug accumulation and possible toxicity unless doses are reduced, dosing interval is increased, or both, depending on the medication

### **Administering Drugs to Children**

- General rules
  - Pediatric medication doses should not be extrapolated from

adult doses

- There are no standardized units for pediatric drug dosing
  - ▶ Most drug dosages are expressed in mg/kg/dose or mg/kg/day; some references list the units in “mg/kg/d.” The “d” may stand for dose or day. Confirm with source
- Some dosages are calculated using body surface area (BSA) in units expressed as mg/m<sup>2</sup>/dose or mg/m<sup>2</sup>/day
  - ▶ The BSA for children and adults (in m<sup>2</sup>) may be calculated using the following:

$$\sqrt{\frac{\text{Ht (cm)} \times \text{Wt (kg)}}{3,600}}$$

- Many drug regimens require modification because of renal insufficiency or failure; usually the dose is decreased, the dosing interval is changed, or both
- The standard method to determine renal status in children is to calculate the creatinine clearance (Cl<sub>Cr</sub>) as described below (**this formula may not provide an accurate estimation of Cl<sub>Cr</sub> for infants < 6 m of age or for patients with severe starvation or muscle wasting**)

$$\text{Cl}_{\text{Cr}} = (\text{K}) \times (\text{L}/\text{S}_{\text{Cr}})$$

Cl<sub>Cr</sub> = creatinine clearance in mL/min/1.733 m<sup>2</sup>

L = length in centimeters

S<sub>Cr</sub> = serum creatinine concentration in mg/dL

K = constant of proportionality that is age specific (Table 39-1)

**Table 39-1. Age-Specific Constant of Proportionality to Determine Creatinine Clearance**

Age (y)	K
Low birth weight < 1	0.33
Full term < 1	0.45
2-12	0.55
13-21 (female)	0.55
13-21 (male)	0.70

- ▶ The change in medication regimen depends on the drug
  - ▷ Common cut-off points for regimen modification are  $Cl_{Cr} \leq 70, \leq 50, \leq 25,$  and  $\leq 10$  mL/minute/1.73<sup>2</sup>
  - ▷ The lower the  $Cl_{Cr}$ , the more severe the renal insufficiency
  - ▷ Consult a pharmacist or pediatric drug reference for specific regimen changes
- Reevaluate dosages at regular intervals to ensure proper adjustment as the child develops
- Ensure that the BSA or body weight dosage is age-appropriate
- When calculating amounts per kilogram, **do not exceed the maximum adult dosage**
- **Always** double-check all computations
- Tips for administering drugs to children
  - Take a confident, positive approach; be kind but assertive
  - Allow the child some control by offering appropriate choices, such as which arm to use for an injection or the flavor of an oral drug chaser (never give the child a choice when none exists)
  - Be truthful about the pain and discomfort associated with the procedure; compare expected sensation with something the child has likely experienced before (eg, a pinch or a pinprick)
  - When explaining how long a procedure will take, remember that children generally do not fully understand the concept of time until approximately age 7–8 years of age; use terms the child can understand (eg, “by the time you count to 3, it will be over”)
  - Children tend to take language literally; avoid using imprecise and potentially frightening jargon, such as, “I’ll have to shoot you again,” “dye” (may be confused with “die”), “put to sleep” (may be confused with euthanizing an animal), “ICU” (“I see you”), and “stool” (confused with something to sit on)
  - Because needles and syringes can produce anxiety, keep them out of the child’s view until ready to administer the medication
- Oral administration
  - Check gag reflex and ability to maintain airway in the

- presence of fluids; assess for nausea and vomiting
- Liquid dosage form ensures more accurate dose for children; use whenever it is available (exceptions include phenytoin, carbamazepine)
  - ▶ If only tablets are available, crush and mix with compatible syrup or food
    - ▷ Crushing may reduce the effectiveness of some drugs
    - ▷ Check with a pharmacist or consult a drug manual before crushing and mixing medications
- To administer oral drugs to infants,
  - ▶ Raise the infant's head to prevent aspiration
  - ▶ Gently press down on the infant's chin with thumb to open the infant's mouth
  - ▶ Administer the dose
    - ▷ Syringe:
      - Place the tip of the syringe in the pocket between the patient's cheek mucosa and gum
      - Administer slowly and steadily to prevent aspiration
    - ▷ Nipple: place medication in rubber nipple and allow infant to suck the contents. **Never** mix medications into a baby's bottle (if the child does not finish the entire bottle, the correct dosage will not be ingested; also, some formulas interfere with drug absorption)
    - ▷ For safety, never refer to a drug as "candy" or a "treat," even if it has a pleasant taste
  - ▶ See Table 39-2 for examples of common oral antibiotic dosing regimens
- Nasogastric route: check nasogastric residuals if giving enteral feedings that interfere with drug absorption
- Rectal
  - Be aware of the special significance of this part of the body to children
  - Toddlers in toilet training will resist the rectal route
  - Older children perceive this as an invasion of privacy and may react with embarrassment, anger, or hostility
  - To reduce a child's anxiety, explain the procedure and reassure that it will not hurt

**Table 39-2. Common Oral Liquid Antimicrobial Medications Used in Children**

Generic Name	Strength (mg/mL)	Average Dose (mg/kg/day)	Interval (h)	Maximum Dose
Amoxicillin	25, 40, 50, 80	Infants < 3 mo old: 20-30	12	2-3 g/day
		> 3 mo old: 25-50	8-12	
		Acute OM due to resistant <i>Streptococcus pneumoniae</i> : 80-90	12	
Amoxicillin + clavulanic acid	25, 40, 50, 80 AMX	Infants < 3 mo old: 30 AMX component	12	Use 25 mg/mL (AMX component) formulation for infants < 3 mo old
		Children < 40 kg: 25-45 AMX component	8-12	Use 4:1 (AMX:CA) formulation (25 or 50 mg AMX/mL) with tid dosing regimen
	120 AMX	> 3 mo old <b>and</b> > 40 kg with multidrug-resistant pneumococcal OM 80-90 AMX component	12	Use 7:1 (AMX:CA) or ES formulation for bid dosing regimen to avoid higher dose of CA
Azithromycin	20, 40	<b>URI and OM</b> in children > 6 mo old: 10 on day 1, followed by 5 on days 2-5	24	500 mg/day for day 1; 250 mg/day for days 2-5
		<b>OM</b> : 10 for 3 days	24	500 mg/day
		or 30 x 1 single dose		1,500 mg/day
		Pharyngitis in children > 2 y old: 12 for 5 days	24	500 mg/day

(Table 39-1 continues)

Table 39-2 continued

Cephalexin	25, 50	25-100	6	4 g/day
Clarithromycin	25, 50	15	12	1 g/day
Clindamycin	15	10-30	6-8	1.8 g/day
Nitrofurantoin	5	Children > 1 mo old: 5-7 UTI prophylaxis: 1-2	6	400 mg/day 100 mg/day
Penicillin V potassium	25, 50	25-50	6-8	3 g/day
Sulfamethoxazole + trimethoprim	8 TMP + 40 SMX	Children > 2 mo old: 6-12 TMP component Serious infection in children > 2 mo old: 15-20 TMP component	12	160 mg TMP component/dose 6-8
Sulfasoxazole	100	Children > 2 mo old: 75 for initial dose then 120-150	4-6	6 g/day

AMX: amoxicillin  
CA: clavulanic acid  
ES: extra strength  
OM: otitis media  
SMX: sulfamethoxazole  
TMP: trimethoprim  
URI: upper respiratory infection  
UTI: urinary tract infection

- Use the fifth finger for administration in children under 3 years old
- After administering the suppository, hold the child's buttocks together for a few minutes to prevent expulsion
- Concurrent critical illness may impair absorption
- Intravenous (IV) infusion
  - To reduce pain at the injection site, offer to use topical anesthetic preparations (eg, lidocaine/prilocaine) with occlusive dressing 30–60 minutes prior to IV access attempt
  - IV access may be more difficult to obtain in young children because they have small veins covered by SQ fat
  - It is difficult to secure IV access in small children
  - There is a greater incidence of infiltration and phlebitis in children than adults; however, this is the most effective route used to deliver medications during critical illness; when properly administered, IV infusion will lead to complete absorption and rapid attainment of drug levels
  - Check compatibility of the solution
    - ▶ Ensure IV medications, flushes, and parenteral nutritional fluids infused in the same IV line are physically and chemically compatible
    - ▶ In infants, hyperosmolar drugs must be diluted to prevent radical fluid shifts that may cause intracerebral hemorrhage
  - Use an arm board when necessary
  - Use soft restraints to minimize movement and risk of kinking or dislodgment
- IM injection
  - Skeletal muscle mass is decreased in newborns and critically ill children
  - Do not use lidocaine as a diluent for drugs needing reconstitution; doing so places the patient at risk for local anesthetic toxicity
  - Reconstitute medication in the highest concentration possible to avoid having to administer two separate injections to give the entire dose
  - The optimum site for IM injection depends on the child's age
    - ▶ < 3 years old: vastus lateralis (lateral thigh) muscle
    - ▶ > 3 years old: gluteus muscle or ventrogluteal area

- Appropriate needle size depends on the child's age and muscle mass
  - ▶ ⅝-inch needle is usually used in young infants
  - ▶ Children or thin, debilitated adolescents may require a 1-inch or smaller (⅝-in.) needle
  - ▶ For most children and adolescents, use a 1-inch or 1½-inch needle, respectively
- Needle gauge is determined by the viscosity of the drug formulation
  - ▶ A 19-gauge needle is used for viscous drugs (eg, penicillin G procaine)
  - ▶ A 21-gauge needle is used for aqueous formulations (eg, penicillin G)
- To avoid unnecessary tissue damage, use the shortest length and highest gauge needle
- The optimum amount of drug to administer via an IM site varies with the child's age, size, and health; volume is generally  $\leq 2$  mL
- Before IM injection
  - ▶ Explain that the injection will hurt, but that the medicine will help
  - ▶ If necessary, restrain the child
  - ▶ Always offer comfort after injection
  - ▶ Rotate sites
- See Table 39-3 for examples of antibiotics that can be given intramuscularly
- SQ injection
  - Infants and children have less SQ fat than adults
  - The SQ injection procedure is similar to IM injection, but uses shorter needles, and volume should be limited to  $\leq 1.5$  mL
  - Use a 25-gauge to 27.5-gauge
    - ▶ For infants and small children  $\leq 3$  years old, use a ⅜-inch or ½-inch needle
    - ▶ For larger children, use a ⅝-inch needle
    - ▶ Obese children and adolescents may require a 1-inch needle
- Inhalants
  - Correct administration depends on child's cooperation
  - Inhalants can be used in children as young as 3 months

**Table 39-3. Common Intramuscular Antimicrobial Medications Used in Children**

Drug Name	Concentration (mg/mL)	Dosage Range (mg/kg/day)	Interval (h)	Maximum Dose	Change Dose/Interval Due to Renal Dysfunction		Comments
					Dysfunction	Yes	
Ampicillin	250	50–400	6	12 g/day	Yes	Yes	3 mEq Na <sup>+</sup> /1 g ampicillin; use within 1 h of reconstitution
Cefazolin	225 or 330*	40–100	6–8	6 g/day	Yes	Yes	2 mEq Na <sup>+</sup> /1 g cefazolin
Cefepime	280	50–150	8	2 g/dose, 6 g/day	Yes	Yes	No dosage adjustment for burn patients
Ceftriaxone	350	50–100	12	2 g/dose, 4 g/day	No	No	3.6 mEq Na <sup>+</sup> /1 g ceftriaxone May cause primary cholelithiasis, nephrolithiasis, and hemolytic anemia; gallstones resolve after discontinuation Not recommended for neonates with hyperbilirubinemia
Gentamicin	40	2.0–3.5 or 5.0–7.5	8 or 24	According to serum levels	Yes	Yes	Peak concentration 4–12 µg/mL (2–3 times higher with once-daily dosing regimen) Trough concentration 0.5–2 µg/mL Contains sulfites, which may exacerbate asthma symptoms May cause cochlear and/or vestibular ototoxicity

\*This concentration is only approved for use with the 1-g vial.

old if an appropriate spacer (valved-holding chamber with mask) is available

- New spacers should be primed with 16 puffs of an albuterol metered-dose inhaler if they are not already static free
- Clean spacer with warm water and mild soap every week to minimize bacterial contamination; do not rinse soap from the inside of holding chamber; the soap film acts as a surfactant and reduces static charge so that medication particles do not adhere to the sides of the chamber
- Use a different spacer for each child (do not share spacers)
- If a nebulizer is to be used to deliver medication, the child needs to wear the mask at all times during drug delivery
  - ▶ Nebulized medicines with a blow-by technique lose 90% of drug delivery
- Common spacer instructions (spacer instructions may vary; read package insert for specific instructions):
  - ▶ Shake canister well before each puff
  - ▶ Properly assemble canister-spacer
  - ▶ Inhale and exhale slowly (if possible)
  - ▶ Place spacer mouthpiece between lips (or mask on face)
  - ▶ Press canister down one time
  - ▶ Inhale slowly (if a whistle sound is heard, patient is inhaling too fast)
  - ▶ Take spacer out of mouth and close mouth
  - ▶ Hold breath for 10 seconds (if unable to hold for 10 sec, exhale and inhale into spacer up to 3 times)
  - ▶ Exhale slowly

### **Emergency Pediatric Drug Therapy**

- Requires quick, accurate dosage calculations and proper administration techniques (Table 39-4)
- Many drugs used for pediatric resuscitation are the same as those used for adults, but with different dosages or concentrations based on weight or BSA
- Emergency drug sheets must be filled out individually and kept at the child's bedside
- Medication administered via peripheral vascular access (followed by a flush), a central line, or IO access is equally efficacious

**Table 39-4. Drugs Used During Pediatric Cardiopulmonary Arrests**

Drug (Generic)	Class	Indications	Dose	Comments
Epinephrine	Catecholamine with $\alpha$ and $\beta$ effects	Cardiac arrest; symptomatic bradycardia; PEA, VF, VT Use infusion postarrest if intermittent boluses failed to restore perfusing cardiac rhythm	Initial: 0.01 mg/kg IV/IO; 0.10 mg/kg via ET Repeat every 3–5 min during resuscitation	The volume given is always 0.10 mL/kg (ie, 0.10 mL of 1:10,000 solution = 0.01 mg/kg) For ET delivery (0.10 mL of 1:1,000 solution = 0.10 mg/kg) Follow with 5-cc NS flush Can cause local tissue necrosis
Atropine	Parasympatholytic agent	Symptomatic bradycardia refractory to optimal airway management	0.02 mg/kg IV, IO, ETT Min dose: 0.1 mg Max dose: child = 0.5 mg adolescent = 1 mg	CO is HR-dependent Symptomatic bradycardia MUST be treated Doses < minimum recommend may cause bradycardia in infants
Adenosine	Antiarrhythmic agent	Reentrant SVT	Initial: 0.1 mg/kg rapid IV/IO bolus Repeat dose: 0.2 mg/kg Max single dose: 12 mg	Short half-life; bolus rapidly and as centrally as possible Follow immediately with 5–10-cc NS flush via 3-way stopcock Be alert for possible asthma exacerbation
Sodium bicarbonate	Alkalinizing agent	Documented severe metabolic acidosis due to prolonged arrest; hyperkalemia; TCA overdose	1 mEq/kg IV or IO May empirically dose 0.5 mEq/kg every 10 min over 1–2 min if ABG results not available	Infuse slowly and only if ventilation is adequate May decrease ionized $Ca^{2+}$ levels May cause $Na^+$ and $H_2O$ overload

(Table 39-4 continues)

Table 39-4 continued

Glucose	Carbohydrate	Hypoglycemia	0.5–1 g/kg IV (1–2 mL/kg 50%; 2–4 mL/kg 25%; 5–10 mL/kg 10%) Max concentration: D <sub>25</sub> W	Hypertonic glucose (D <sub>25</sub> W or D <sub>50</sub> W) may harden peripheral veins if it extravasates Do not exceed 12.5% glucose in neonates
Calcium chloride	Calcium salt	Hypocalcemia, hyperkalemia	0.2 mL/kg of elemental calcium (20 mg/kg) Repeat after 10 min prn if ionized calcium deficiency persists	Infuse no faster than 100 mg/min. May induce bradycardia or asystole, especially if patient is also on digoxin Extravasation can cause chemical burn or sclerosis of peripheral veins
Naloxone	Narcotic agonist	Narcotic poisoning	<b>Birth–5 y (≤ 20 lb):</b> 0.1 mg/kg IV/ETT > 5 y (≥ 20 lb): 0.4–2 mg/dose IV/ETT <b>Continuous infusion:</b> 0.04–0.16 mg/kg/h, titrated to effect	Rare side effects usually related to abrupt narcotic reversal Administer with caution immediately after birth to infants of addicted mothers to avoid abrupt withdrawal and seizures in infant
Magnesium sulfate	Antiarrhythmic agent; electrolyte	Hypomagnesemia; torsades de pointes	25–50 mg/kg IV/IO (max dose: 2 g/dose)	Monitor serum Mg <sup>2+</sup> level Use with caution in patients also on digoxin (can lead to heart block)
Lidocaine	Antiarrhythmic agent	Ventricular dysrhythmias	<b>Loading:</b> 1 mg/kg <b>Infusion:</b> 20–50 µg/kg/min (concentration: 120 mg lidocaine/100 mL D <sub>5</sub> W)	Toxic levels can cause myocardial, circulatory, and/or CNS depression Metabolized by the liver

**Table 39-4** notes:

ABG: arterial blood gas  
CNS: central nervous system  
CO: cardiac output  
D<sub>5</sub>W: 5% dextrose in water  
D<sub>25</sub>W: 25% dextrose in water  
D<sub>50</sub>W: 50% dextrose in water  
ET: endotracheal  
ETT: endotracheal tube  
HR: heart rate  
IO: intraosseous  
IV: intravenous  
NS: normal saline  
PEA: pulseless electrical activity  
prn: pro re nata (as needed)  
SVT: supraventricular tachycardia  
TCA: tricyclic antidepressant  
VF: ventricular fibrillation  
VT: ventricular tachycardia

- The endotracheal route may be used to administer epinephrine, atropine, and lidocaine
  - Usually the dose is 1½–10-fold that for the IV route
  - Follow drug administration with a 5-cc flush of normal saline to aid in drug delivery to the peripheral airways
  - Endotracheal administration of drugs is no longer recommended by the Neonatal Resuscitation Program
- Usual maximum volume for IM administration:
  - Neonate: 0.5 mL
  - Children: 1–2 mL
  - Adult: 2–3 mL

**Further Reading**

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