Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics

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Learning Objectives

1. Analyze alterations in pharmacokinetics (PK) and pharmacodynamics (PD) that result in changes in response to drug therapy in neonates, infants, children, and adolescents.
2. Summarize pharmacogenomic considerations in pediatric patients.
3. Identify medications that cause pediatric-specific adverse reactions.
4. Differentiate routes of administration related to pediatric care and their PK and PD implications.
5. Evaluate age-associated differences in pathophysiology and clinical manifestations of disease dynamics across patient populations.

Abbreviations

ADR	Adverse drug reaction
DME	Drug-metabolizing enzyme
DT	Drug transporter
GA	Gestational age
PD	Pharmacodynamics
PG	Pharmacogenomics
PK	Pharmacokinetics
PMA	Postmenstrual age
Vd	Volume of distribution

Self-Assessment Questions

Answers and explanations to these questions may be found at the end of this chapter.

1. Which best describes cytochrome P450 (CYP) 3A7 enzyme activity in term neonates?
   A. Higher activity than in adulthood.
   B. Absent until 9–12 months of age.
   C. The primary CYP3A isoform in adolescents and adults.
   D. Low initial activity with a gradual increase in activity.

2. Which is most likely to cause an altered pharmacodynamic (PD) drug response in infants?
   A. Skin surface area.
   B. Pulmonary surface area.
   C. Increased metabolic rate.
   D. Differences in disease etiology and pathophysiology.

3. Which most likely complicates intramuscular drug delivery in neonates?
   A. High total body water content.
   B. Increased first-pass metabolism.
   C. Dose volume.
   D. Decreased binding proteins.

4. Which best describes renal drug clearance changes that occur through glomerular filtration rate (GFR) maturation?
   A. Most in utero developmental changes in GFR occur between 36 and 40 weeks' gestation.
   B. Changes subject to induction of GFR by exposure to drugs are proximal tubule OAT (organic anion transporters) or OCT (organic cation transporter) substrates.
   C. Renal drug clearance values in children approach those of adults by 2 weeks of age.
   D. Maternal creatinine "contaminates" neonatal serum creatinine (SCr), preventing its use for determining GFR in infants for the first few days of life.

5. Many oral drugs metabolized by CYP enzymes require higher milligram per kilogram doses in 2-year-old toddlers than in adults. Which mechanism best describes this need for higher doses in toddlers?
   A. Reduced drug receptors requiring higher drug concentrations.
   B. Increased CYP content per gram of pediatric liver.
   C. Reduced first-pass metabolism in toddlers.
   D. Larger liver weight/total body weight ratio in toddlers.

6. Which best describes the impact of CYP2D6 polymorphisms on opioid therapy?
   A. *CYP2D6* genotype is only an important consideration in ultra-metabolizers who need larger codeine doses.
   B. CYP2D6 genotype has a bigger impact on morphine than on codeine dosing requirements.
   C. Higher morphine concentrations occur in CYP2D6 ultra-metabolizers receiving codeine.
   D. CYP2D6 poor metabolizers have exaggerated opioid effects from codeine.

7. Which best describes body composition at birth in term newborns?
   A. Lower albumin and α_1-acid glycoprotein concentrations lead to larger weight normalized (liters per kilogram) volume of distribution (Vd).
   B. Total body water is lower in newborns than older populations.
   C. A greater portion of total body water is intracellular.
   D. High body fat requires higher loading doses for lipophilic drugs.

8. You are caring for a neonate in the neonatal intensive care unit. Which is the most important consideration for neonates regarding drug absorption?
   A. Gastric emptying time is decreased during the first week of life.
   B. Transdermal absorption is greater in neonates because hydration is decreased and skin thickness is increased.
   C. Low gastric acid secretion in newborns can impair drug absorption for drugs that require a low pH for absorption.
   D. Intramuscular absorption is predictable and often used because intravenous access can be limited in neonates.

9. When determining the correct dose for aminoglycosides, which option best describes the change you would most likely see in neonates compared with adults?
   A. The changes in Vd and clearance have opposite effects on half-life, resulting in similar half-lives in neonates and adults.
   B. Vd does not change in neonates, but clearance is higher for neonates than for adults.
   C. Clearance is typically lower in neonates because of immature renal function.
   D. Clearance varies greatly among individual neonates; therefore, no consistent comparative differences between adults and neonates can be made.

I. INTRODUCTION

A. This chapter will provide an overview of the developmental clinical pharmacology, including pharmacokinetics (PK), pharmacodynamics (PD), pharmacogenomics (PG), and disease progression, that affects the use of medications in children.

B. Normal human gestational age (GA) is 40 weeks from the mother's last menstrual period.

C. Babies born at 37–42 weeks' gestation are considered term.

D. Babies born at less than 37 weeks' gestation are considered preterm.

E. The degree of prematurity is further classified by birth weight.
   1. LBW (low birth weight) less than 2500 g (less than 35 weeks GA)
   2. VLBW (very low birth weight) less than 1500 g (less than 30 weeks GA)
   3. ELBW (extremely low birth weight) less than 1000 g (less than 27 weeks GA)

F. Maturation in neonates and infants is often expressed as postmenstrual age (PMA), which is the GA at birth added to their PNA (postnatal age). For example, an infant born at 32 weeks with a PNA of 8 weeks would have a PMA of 40 weeks.

G. Key pediatric age group classification is summarized in Table 1.

Table 1. Classification of Pediatric Age Groups

Age Classification	Definition
Gestational age (GA)	Time from conception until birth
Postnatal age (PNA)	Chronologic age since birth
Premature neonate	Born at GA < 37 wk
Term neonate	Born at GA 37–42 wk
Neonate	Infant 0–1 mo old
Infant	Infant 1 mo to 1 yr old
Toddler	1–3 yr old
Child	1–12 yr old
Adolescent	13–18 yr old
Adult	> 18 yr old

H. Adolescents can also be characterized by "biologic" age using the Tanner scale, which is a scale of physical development based on secondary sexual features that appear during puberty.
   1. Age can have significant effects on PK, PD, and disease presentation-progression.

II. PHARMACOKINETICS

A. Absorption:
1. Key equations:
   a. $F_{PO} = dose_{IV} \times AUC_{PO}/dose_{PO} \times AUC_{IV}$
   b. $F_H = 1 - E_H$
   c. $F = F_A \times F_G \times F_H$
   d. Tmax = ln(Ka/ K)/(Ka − K) for single dose
   F_{PO} = fraction of bioavailability
   AUC = area under the concentration versus time curve
   F_H = fraction of bioavailability as the result of hepatic first-pass metabolism
   E_H = hepatic extraction fraction
   F_A = fraction of the dose that is actually absorbed
   F_G = fraction of bioavailability as the result of gut (enterocyte) first-pass metabolism
   Tmax = time of maximal concentration
   Ka = absorption rate constant
   K = elimination rate constant
2. Oral absorption is characterized by rate (Tmax, Ka) and extent (F), and age can affect both rate and extent. F effects can be through F_H, F_A, or F_G.
3. Factors that may affect gastro-enteral absorption:
   a. Gastric acid production:
      i. Gastric acid production is reduced in infants, causing higher pH.
      ii. Term infants: Gastric pH is neutral at birth, falls to pH 2–3 within hours after birth, and returns to neutral pH at around day 10. It slowly declines thereafter does not achieve adult values, pH 2–3, until 3 years of age.
      iii. Preterm infants do not produce significant gastric acid until 32 weeks GA.
      iv. An infant's gastric pH can also be affected by feeding and illness.
      v. Low acid production can increase the absorption of acid labile drugs (e.g., didanosine) and reduce the absorption of drugs that need acid for absorption (ketoconazole)
   b. Gastro-enteral transit time
      i. Gastric emptying time is significantly prolonged during the first week of life. Slower movement may allow more time for drugs to be absorbed.
      ii. Premature infants have slower gastric emptying than do term infants.
      iii. Gastric emptying is delayed and irregular until 6–8 months of age.
      iv. Gastro-enteral transit time is reduced in older infants and children up to about 3 years of age relative to that of adults.
      v. Drug absorption is influenced by gastroenteritis, diarrhea, diet, and other drugs that alter gastro-enteral transit time.
   c. Initial bacterial colonization of the colon occurs within the first few days of life. However, the gut microbiome changes dramatically over the first year of life. These bacteria can produce enzymes such as glucuronidases that can alter bioavailability or promote enterohepatic recycling of drugs excreted in the bile as glucuronide metabolites.
   d. Bile acids and lipolytic activity are reduced in term infants, and drug solubility and F_A may be affected.
   e. Drug-metabolizing enzymes (DMEs) and drug transporters (DTs), including CYP3A, the uridine 5'-diphospho-glucuronosyltransferase enzyme (UGT), and P-glycoprotein in the gut, may be reduced in young infants but increase to levels at or above adult activity in the first few years of life.
   f. Pediatric diseases of the gut – Short gut syndrome and GERD (gastroesophageal reflux disease) may affect the rate and extent of absorption.

g. Diet can affect drug absorption.
   i. Calorie-dense foods may slow transit time.
   ii. Complex fats and fiber may bind drugs, which will result in slowing or preventing absorption.
   iii. Some drugs require fasting or a high-fat diet for optimal absorption in adults. These requirements may not be achievable in infants and young children.

h. Pediatric formulations, especially extemporaneous formulations, may not be bioequivalent to adult formations. Crushing adult formulations or mixing pediatric formulations in applesauce or other infant foods may also affect F_A.

4. Factors that may affect rectal absorption:
   a. In general, half of rectal blood flow bypasses the liver and reduces potential first-pass metabolism.
   b. Premature expulsion of the dosage form will decrease absorption.
   c. Rectal space will limit the volume of drug that can be given.
5. Factors that may affect intramuscular absorption:
   a. Intramuscular absorption is variable in neonates and premature neonates.
   b. Reduced muscle mass may result in reduced intramuscular absorption because of decreased drug dispersion within the muscle.
   c. Reduced muscle tone may result in less blood flow and subsequently prolonged absorption time.
   d. Infants and neonates have poor perfusion to muscle tissue and therefore have variable intramuscular absorption.
   e. The muscle blood flow relative to muscle mass is greater in young children than in adults and may result in more rapid intramuscular absorption.
   f. Intramuscular dose amounts may be limited by the volume that can be administered.

Table 2. Intramuscular Administration Volume Allowances

Age	Patient's Body Weight (kg)	Maximum Volume (mL)
Premature neonate	Up to 2.5	0.5
Neonates and infants	2.5–4	1
Toddler	4–12	1–1.5
Child	12–40	1.5–2
Adolescent	> 40	2.5–3

6. Factors that may affect percutaneous absorption:
   a. Neonatal skin is thinner and relatively weaker as a barrier, which allows an increase in drug and vehicle absorption through the skin.
   b. Neonatal skin perfusion is increased, which may enhance drug absorption.
   c. A higher insensible water loss occurs through the neonatal skin, which can result in an increased absorption of drugs through the skin.
   d. Body surface area/weight ratio is greater in neonates, infants, and young children than in adults; therefore, a greater amount of drug relative to body weight can be absorbed.
   e. Toxicity can occur with topical products in infants and young children because of enhanced absorption (e.g., hexachlorophane = pHisoderm – spongiform myelinopathy; lindane – neurotoxicity including seizures) and altered PD.
7. See Routes of Administration in section V, "Applied Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics."

B. Distribution
   1. Key equations:
      a. Vd = dose/Cmax for intravenous bolus single dose
      b. Vd = dose/(Cmax − Cmin) for intravenous bolus at steady state, where Cmax is the maximum concentration and Cmin is the minimum concentration
      c. Vd = CL/K, where CL is clearance.
      d. Vd = F x dose/(AUC x K)
      e. $Vd \times C = Vd_u \times C_u$
         Vd = volume of distribution
         Cmax = maximum concentration
         Cmin = minimum concentration
         CL = clearance
         F = bioavailability fraction
         AUC = area under the concentration versus time curve
         K = elimination rate constant
         Vd_u = volume of distribution of unbound drug
         C = concentration
         C_u = unbound concentration
   2. Definition: Vd is a proportionality constant that relates the amount of drug in the body to the drug concentration. Vd is matrix-specific and is typically determined for total serum or plasma concentrations but can be determined for whole blood or unbound drug concentrations (Cu values). The Vd values for a drug will be different depending on the matrix selected.
   3. Physiologic factors in body composition affect the distribution of drugs.
      a. Changes in fluid compartments and body composition will affect the spaces into which a drug can be distributed. Neonates have higher percent total body water and lower percent muscle mass than older populations.
      b. The Vd may be increased in neonates for some drugs such as water-soluble drugs (e.g., gentamicin and β-lactam antibiotics), which contributes to a longer half-life of these agents in neonates. Therefore, water-soluble drugs may require higher doses per weight in infants to achieve target peak/trough concentrations.
      c. Adipose tissue functions as a reservoir for lipophilic drugs. As age-related changes occur in the amount of adipose tissue, the distribution of lipophilic drugs changes. The very low body fat content in preterm infants places them at a potential risk of high serum concentrations of lipophilic drugs.

Table 3. Fluid Compartment Estimates as a Function of Age

Age	Total Body Water (%)	Extracellular Fluid (%)	Adipose Tissue (%)
Premature neonate	92	50	1–5
Term neonate	75	35	12–16
3 mo	73	35	35
1 yr	59	25	30
Adult	60	19	20

d. Protein binding can affect free or unbound drug concentrations in plasma.
   i. In general, albumin binds with acidic drugs, and α_1-acid glycoprotein binds with basic drugs.
   ii. The amount of binding proteins (e.g., albumin and α_1-acid glycoprotein) is reduced and variable in neonates and some infants, thereby increasing the free fraction of active drug. This can result in larger weight normalized (liters per kilogram) Vd values in neonates and young infants for drugs with significant protein binding. Binding protein concentrations typically reach adult concentrations by 10–12 months of age.
   iii. The available proteins may have a decreased affinity for drug binding.
   iv. There is competition for certain binding sites among drugs and endogenous compounds (e.g., bilirubin)—for example, the development of kernicterus secondary to the displacement of bilirubin by certain drugs (see Table 4).
e. Cardiac output and regional blood flow can also alter drug disposition. Cardiac output and regional blood flow are more variable in pediatric patients than in adults. Infants and young children have a larger proportion of body weight as a brain mass and have higher cerebral blood flow than adults.

4. Drug factors
   a. The pKa (acid dissociation constant) of the active drug affects the absorption, together with trapping the ionized form on one side of a membrane. Neonates typically have a lower blood pH during the first 20 minutes of life, which can be prolonged in those experiencing respiratory distress.
   b. The molecular weight and water solubility can affect drug distribution.
5. Drug transporters (DTs): P-glycoprotein (also known as MDR1) is the most prominent member of energy-dependent efflux pumps in cell membranes and represents an important component of the blood-brain barrier. DTs also play a critical role in enterocyte, renal, and hepatic excretion. In neonates and infants, P-glycoprotein and other DT tissue expression is reduced, and in children, the activity among tissues is variable and less well defined.

C. Metabolism
1. Key equations:
   a. $C_0 = F \times dose/Vd$ (for the first dose)
   b. $CL = F \times dose/AUC$
   c. $CL = K \times Vd$
   d. $CL = R_{in}/C_{ss}$ for continuous infusion at steady state
   e. $CL_{total} = CL_{renal} + CL_{hepatic} + CL_{other}$
   f. $CL = Q_H \times (fu \times CL_{int})/[Q_H + (fu \times CL_{int})]$
   g. $t_{1/2}$ (half-life) $= 0.693/K$
   h. $t_{1/2} = 0.693 \times Vd/CL$ (clearance)
   i. $K = \ln(C_1/C_2)/(t_2 - t_1)$ during the log-linear elimination phase
   j. Rate of elimination = $Vmax \times Conc/(K_m + Conc)$, where K_m is the Michaelis-Menton constant.
2. Hepatic metabolism
   a. At birth, hepatic metabolism is slower because of underdeveloped DMEs and uptake DTs. This results in most drugs' metabolism being reduced at birth. Even lower DME activity occurs in preterm than in term infants.
   b. Individual drug metabolism pathways have different levels of activity at birth and variable rates of development. This results in large interpatient differences in neonatal and infant drug-metabolizing capacity.
   c. The liver constitutes a greater percentage of total body weight and receives greater blood flow during childhood than during adulthood. As the child grows into an adult, the liver becomes a smaller proportion of the total body weight. This often results in larger weight "normalized"

clearance (liters per hour per kilogram) in children (after ontogeny of enzymes) than in adults. To account for the larger liver size and greater blood flow in children, clearance is often "normalized" to body surface area (BSA) or "allometric weight" weight$^{0.75}$ to achieve more similar clearance values across the pediatric age continuum.

d. With allometric scaling, because Vd is proportional to weight but clearance is proportional to weight$^{0.75}$, the half-life is shorter in young children than in older children, as for aminoglycosides and vancomycin.
e. Low DME activity of a specific pathway in neonates can lead to the switching of the primary DME pathway to another DME pathway or to primary renal excretion. For example, caffeine, primarily a CYP1A2 substrate in adults, is primarily eliminated renally in neonates because of the lower activity and slower maturation of CYP1A2 than renal clearance development.
f. The primary phase I enzymes (such as CYP) are listed and discussed in Table 4.
g. The immature CYP system has additional factors that will influence its ability to metabolize drugs.
    i. Genetics: The PG effects on enzyme metabolism are discussed in the Pharmacogenomics section.
    ii. Maternal hormones: The enzymes remain under the influence of maternal hormones for 1–2 months after birth, although they may not have great importance in drug metabolism.
    iii. Environment: This broad category may include an exposure to chemicals in the environment and pollutants in the drinking water or smoke, whether industrial or tobacco.
    iv. Drugs: Concurrent medications and/or possibly illicit maternal drugs

Table 4. Developmental Differences of Important CYP Drug-Metabolizing Enzymes and Their Effects

CYP Enzyme	Effect	Examples
1A2	• Minimal fetal activity • Gradual increase in activity in infancy; exceeds adult activity during childhood and then returns to adult activity • Inducible by many environmental factors • CYP1A2 drug interactions may not be apparent in newborns because of low activity	Methylxanthines
2B6	• Activity reduced at birth – ~25% of induced mature activity • Most of activity gained by 3–4 mo • Clinically relevant functional genetic polymorphisms exist and occur more commonly in African Americans than in whites	Nonnucleoside reverse transcriptase inhibitors, methadone
2C9	• Very low activity at birth • Exceeds adult activity during childhood and then returns to adult activity • Clinically relevant functional genetic polymorphisms exist	Nonsteroidal anti-inflammatory drugs, phenytoin
2C19	• Activity increases rapidly within the first 2 wk of life • Clinically relevant functional genetic polymorphisms exist	Antiepileptics; PPIs
2D6	• Low to absent in fetus • Rapid acquisition of activity (about 2 wk); mature by 10 yr • Clinically relevant functional genetic polymorphisms exist including copy number variation leading to ultra-metabolizers	Many drugs; codeine, β-blockers, antidepressants

Table 4. Developmental Differences of Important CYP Drug-Metabolizing Enzymes and Their Effects *(continued)*

CYP Enzyme	Effect	Examples
3A4	• Very low hepatic activity at birth • Rapid development during the first month of life while CYP3A7 activity wanes • Present in the gut and responsible for F_G for many drugs • No prominent functional genetic polymorphisms • Many enzyme inducers and inhibitors significant alter CYP3A activity	Many drugs; midazolam, statins, glucocorticoids
3A5	• Similar developmental pattern assumed as with CYP3A4 • Significant substrate overlap with CYP3A4 • Clinically relevant functional genetic polymorphisms exist with greater liver expression in African Americans than in whites	Many drugs; midazolam, statins, glucocorticoids
3A7	• High fetal and newborn activity • Primary CYP3A isoform at birth • Substrate specificity similar to CYP3A4/5 but, in general, efficiency lower than CYP3A4/5 • Combined CYP3A4/5/7 activity is ~20%–30% of mature values at birth in term infants • Preterm infant CYP3A4/5/7 activity is only 60% of term infants • Minimal CYP3A7 activity after the first month of life	Many drugs

PPI = proton pump inhibitor.

h. Phase II enzymes facilitate the elimination of compounds from the body, although not every drug will undergo phase II metabolism.
   i. In general, this type of biotransformation renders the compounds inactive and more polar to increase water solubility and excretion.
   ii. Phase II enzymes found in the liver are the major pathway for conjugating and eliminating most exogenous molecules in humans.

i. Glucuronidation is accomplished by UGT. Several different UGT isoforms involved in drug metabolism have substrate sensitivity, including UGT1A1, UGT1A6, and UGT2B7. Glucuronidation activity of acetaminophen, morphine, and zidovudine metabolism is reduced in newborns and young children compared with adults. The reduced conjugation activity of UGT is the reason for chloramphenicol toxicity in infants.

j. Acetylation is accomplished by acetyltransferase enzymes, which have reduced activity in infants.

k. Sulfation is accomplished by sulfotransferase enzymes, which have significant activity in infants.

l. Methylation is accomplished by methyltransferase enzymes.

3. Renal metabolism: In addition to their presence in the liver, CYP3A and some phase II enzymes can be found in the kidneys. The enzymes for glucuronidation, methylation, and sulfation are found in the kidneys.

4. Pulmonary metabolism: Similarly, some phase II enzymes are found in the lungs. The enzymes for acetylation, glucuronidation, and methylation are found in the lungs.

5. Nonlinear metabolism – Some drugs may be dosed above their K_m and have nonlinear metabolism. Ethanol and phenytoin are the two most commonly encountered examples of this phenomenon. For phenytoin, modest changes in dosing or absorption can lead to very large changes in steady-state drug concentrations.

Patient Cases

1. P.D. is a 10-day-old term infant in the neonatal intensive care unit being treated for seizures. P.D. continues to have seizures despite phenobarbital therapy with a therapeutic phenobarbital concentration of 28 mcg/mL. The intern wants to load P.D. with phenytoin and begin a maintenance dose of phenytoin. Which is the most appropriate statement regarding phenytoin use in this infant?
   A. Phenytoin should not be used in neonates younger than 2 weeks because of the risk of kernicterus.
   B. Phenytoin is highly protein bound, and with the altered binding in newborns, monitoring free drug concentrations may be considered.
   C. Phenobarbital can induce phenytoin metabolism, so smaller maintenance doses are usually needed.
   D. Genotyping before therapy can predict infants likely to experience phenytoin-induced liver toxicity.

2. B.G. is a 2-year-old boy (weight 12 kg) with a methicillin-resistant *Staphylococcus aureus* (MRSA) pulmonary infection being treated with vancomycin 120 mg intravenously every 8 hours. His SCr is 0.3 mg/dL. His measured vancomycin trough is 4.0 mcg/mL before the fourth dose. Which is most accurate regarding this toddler's vancomycin pharmacokinetics?
   A. Like most pediatric patients, he has a higher hepatic vancomycin clearance than an adult and thus requires higher doses.
   B. High renal clearance and short half-life of vancomycin in children require more frequent dosing than in adults to achieve similar troughs.
   C. His target therapeutic AUC is lower because of the lower protein binding, and free (unbound) vancomycin concentrations should be measured before increasing his dose.
   D. Because renal function matures by 2 years of age, he should be placed on the adult equivalent dose of 15 mg/kg every 12 hours.

3. T.G. is a 2-year-old girl receiving valproic acid and phenytoin for treatment of her seizure disorder. Her SCr is 0.2 mg/dL, albumin 3.4 g/dL and total bilirubin 0.1 mg/dL. Which statement is most accurate about her anticonvulsant regimen?
   A. Liver function tests can be monitored less frequently in children than in adults because there is a decreased risk of hepatotoxicity in children.
   B. Valproate can displace phenytoin from albumin and lead to increased phenytoin free fraction.
   C. Induction of CYP enzymes by valproate will likely lead to lower phenytoin concentrations.
   D. Her CYP2D6 genotype can be used to predict the valproate dose she needs to achieve therapeutic concentrations.

4. A.K. is a 2-month-old girl (weight 5 kg) with an SCr of 1.7 mg/dL. She is initiated on tobramycin and given a loading dose of 15 mg. A tobramycin concentration 6 hours after the loading dose is 7.2 mcg/mL, and a subsequent tobramycin concentration 18 hours post-dose is 1.8 mcg/mL. A second dose of 10 mg is given immediately after the second level. Which best depicts her tobramycin concentration 6 hours after the second dose?
   A. 9.0 mcg/mL.
   B. 7.2 mcg/mL.
   C. 5.7 mcg/mL.
   D. Cannot be determined by the information given.

D. Elimination
   1. Key equations:
      a. fe = $Ae_{(0\text{-}inf)}$/dose
      b. CL_{renal} = fe x CL_{total}
      c. CL_{renal} = $Ae_{(0\text{-}inf)}$/$AUC_{(0\text{-}inf)}$: Single
      d. CL_{renal} = $Ae_{(0\text{-}tau)}$/$AUC_{(0\text{-}tau)}$: At steady-state
      fe = fraction excreted in urine
      Ae(0-inf) = total amount excreted in the urine
      CLrenal = renal clearance
   2. Renal elimination:
      a. The kidneys are immature in both structure and function at birth.
      b. Kidneys at birth receive only 5%–6% of cardiac output compared with 15%–25% in adults.
      c. Renal blood flow is about 12 mL/minute at birth compared with 1100 mL/minute in adults, and it increases during the first year of life.
      d. GFR is widely accepted as the best indicator of renal function.
      e. GFR is directly proportional to GA beyond 34 weeks GA.
      f. GFR estimations for neonates:
         i. 10–15 mL/minute/m^2 in term
         ii. 5–10 mL/minute/m^2 in preterm
         iii. GFR typically doubles during the first 1–2 weeks of life, followed by more gradual gains during the next several months.
      g. In 1976, the original Schwartz equation was developed, with creatinine measured by the Jaffe reaction. However, today, newer methods are used to measure creatinine, and the original Schwartz formula may overestimate the GFR. Therefore, in 2009 and 2012, the new Schwartz bedside and full equations were developed. However, these equations are only applicable in those 1–18 years of age.
      h. There are limitations in measuring renal function in pediatric patients, especially in neonates during the first few days of life, because SCr reflects the measurement of maternal creatinine.

Table 5. Schwartz Equations for Estimating GFR

Bedside Schwartz Equation (1–18 yr)
GFR (mL/minute/1.73 m^2) = 0.41 x L/SCr
L = length (cm)
SCr = serum creatinine (mg/dL)
Schwartz Cystatin C Equation (1–18 yr)
GFR (mL/min/1.73 m^2) = $70.96/(CysC)^{0.931}$
CysC = Cystatin C (mg/L)
Original Schwartz Equation
GFR (mL/minute/1.73 m^2) = (*K* x L)/SCr
L = length (cm)
SCr = serum creatinine (mg/dL)

Table 5. Schwartz Equations for Estimating GFR *(continued)*

Age	K =
< 1 yr old, low-birth-weight infant	0.33
< 1 yr old, full-term infant	0.45
2–12 yr old child	0.55
13–21 yr old female	0.55
13–21 yr old male	0.7

GFR = glomerular filtration rate.

i. Developmental models to estimate GFR maturation have been proposed by Rhodin according to PMA and by Johnson according to BSA:
   i. Rhodin 2009
   ii. GFR (mL/min) = 121 x $PMA^{3.4}/[PMA^{3.4} + 47.7^{3.4}]$ x $(WT/70)^{0.75}$
   iii. Johnson 2006
   iv. GFR (mL/min) = -6.1604 x BSA^2 + 99.054 x BSA -17.74

j. Tubular secretion
   i. Immature at about 20% of adult capacity at birth in term infants
   ii. Increases 2-fold during the first week of life and continues to increase several-fold during the first year of life
   iii. Many transporters involved in tubular secretion work in serial with each other. Thus, both basolateral and apical transporter activity is needed for drug secretion. This makes it difficult to characterize the individual developmental patterns for individual transporters on net renal secretory drug clearance.
   iv. Key renal DTs include those from the OATs (organic anion transporters), OCTs (organic cation transporters), MATE (multi-antimicrobial extrusion protein), MDR1 (multidrug-resistant protein 1, also known as P-glycoprotein), and MRP (multidrug resistance-associated protein) superfamilies.

3. Pulmonary elimination: Lung changes, particularly during the first 3 years of life, affect drug disposition. This includes growth of the internal surface area.

III. PHARMACODYNAMICS

A. Key Equations
   1. Maximum response (Emax) model: Effect = Emax x $C/(EC_{50} + C)$, where C is concentration and EC_{50} is concentration that produces half of the maximal effect.
   2. Sigmoid Emax model: Effect = Emax x $C^g/(EC_{50}{}^g + C^g)$
      a. The Emax model indicates diminishing effects as the drug concentrations exceed the EC_{50}. The drug concentration that generates half of the Emax (the EC_{50}) needs to be increased 9-fold to increase the effect from 50% to 90%.
      b. According to the Emax and Sigmoid Emax models, the concentrations that generate 20%–80% of maximal effects have a relatively linear relationship between drug effect and the log of the concentration.

B. Definition: Whereas PK considers what the body does to the drug, PD represents what a drug does to an individual or a body function. Individual drug effects are variable, but pediatric compared with adult PD are characterized by differences in receptors, disease etiology, paradoxical effects of drugs, altered toxicity, and direct drug effects on growth and development.

1. Altered drug responses may be caused by the following drug receptor differences.
   a. Sensitivity – Pediatric patients' receptors may be more or less sensitive to stimulation. In addition, the importance of a particular pathway in regulating a physiologic function may be different in pediatric patients.
   b. Affinity – Pediatric patients' receptors may have a greater affinity for drugs.
   c. Numbers – Pediatric patients may have fewer receptors.
2. Paradoxical drug effects may occur in children. An example of a commonly described effect in some children is the excitatory consequences associated with antihistamines, rather than the more typical sedation.
3. Drugs may affect growth and development.
   a. Corticosteroids
   b. Tetracycline
   c. Growth hormone
   d. Drugs that affect appetite
4. Assessment of PD and Disease Dynamics in Pediatric Patients
   a. The biomarker used to diagnose or monitor drug effects in pediatric patients may be different from that in adult patients (e.g., pain scales, tuberculosis culture from gut vs. lungs, pulmonary function assessments).
   b. Normal ranges and therapeutic goals may be different (e.g., blood pressure, heart rate, $CD4^+$ cells).
   c. Etiology and pathophysiology of diseases (e.g., hypertension – usually secondary, febrile seizures, neonatal apnea/bradycardia, central nervous system bleeds)
   d. Diseases and toxicities exclusive to pediatric patients (e.g., Kawasaki disease, Reye syndrome, patent ductus arteriosus [PDA], absence epilepsy, many childhood cancers)
   e. Altered disease dynamics (hypoxemia-induced neonatal seizures and PDA often have rapid healing, whereas untreated HIV infection has very rapid progression)

Table 6. Selected Known Pediatric-Specific Adverse Drug Reactions and Recommendations

Drug	Reaction	Recommendations
Aspirin	Reye syndrome is a serious condition that causes acute brain damage and liver failure. It has been associated with the use of aspirin after a viral illness	Avoid the use of aspirin as an antipyretic or analgesic in pediatric patients during or after a viral illness
Sulfonamide drug class, dicloxacillin, cefoperazone, and ceftriaxone	Kernicterus was reported in neonates receiving sulfonamide drugs, which displace bilirubin from protein-binding sites in the blood to cause hyperbilirubinemia, resulting in the deposition of bilirubin in the brain, encephalopathy, and death in neonates and infants	Ceftriaxone should be used with caution in high-risk jaundiced infants. Sulfonamides should be avoided in neonates and infants. Oral doses of sulfamethoxazole and trimethoprim are unlikely to cause kernicterus
Fluoroquinolones (FQs) drug class	Development of permanent lesions of the cartilage of weight-bearing joints and other signs of arthropathy in immature animals has been reported	The use of FQs in children may be justified if the infection is caused by a multidrug-resistant pathogen when there is no safe and effective alternative and if oral therapy is preferred. In addition, topical FQs may be acceptable in children for tympanostomy tube–associated otorrhea. Furthermore, FQs may be used if there are concerns for antimicrobial resistance, toxicity, or needed tissue perfusion

Table 6. Selected Known Pediatric-Specific Adverse Drug Reactions and Recommendations *(continued)*

Drug	Reaction	Recommendations
Chloramphenicol	"Gray baby syndrome" has been described as a constellation of symptoms, including vomiting, poor feeding, respiratory distress, abdominal distension, cyanosis, ashen color, hypothermia, and death. This syndrome was reported in newborns who received chloramphenicol and is caused by the immature UGT metabolism and enhanced bioavailability of chloramphenicol when given to neonates and infants	Chloramphenicol should not be used in neonates and infants
Tetracycline drug class	Dental staining and darkening of permanent teeth has been reported in patients receiving tetracyclines during the time of tooth crown formation	Tetracycline drugs are contraindicated in pregnant women, nursing mothers, and children < 8 yr
Valproic acid	Valproic acid–associated hepatotoxicity has its highest risk in children < 2 yr. It is caused by several PK factors (e.g., increase in toxic metabolites, inhibition of mitochondrial β-oxidation, depletion of hepatic free coenzyme A reserves, carnitine deficiency, and inborn mitochondrial disorders)	Caution should be used in patients < 2 yr receiving valproic acid
Lopinavir/ritonavir	Serious cardiovascular events (bradycardia, heart block, heart failure) and renal failure seen in the first few days of life. Ethanol and propylene glycol excipients may be contributory	Should be avoided in infants < 14 days of age and < 42 wk PMA
Glucocorticoid steroids	Contribute to slow growth in children. Systemic dexamethasone use in infants is associated with reduced head circumference and increased cerebral palsy	Limit systemic steroid use to the lowest dose and duration, possible
Antidepressants	An increased risk of suicide among adolescents has been reported	Antidepressants should be used with caution in children and adolescents
Propylene glycol	Hyperosmolality in infants caused by the administration of products containing propylene glycol has been reported	Caution should be used to limit the amount of propylene glycol to very small neonates and infants

Table 6. Selected Known Pediatric-Specific Adverse Drug Reactions and Recommendations *(continued)*

Drug	Reaction	Recommendations
Benzyl alcohol	A syndrome that includes metabolic acidosis, seizures, neurologic deterioration, gasping respirations, hepatic and renal abnormalities, cardiovascular collapse, and death was described in premature infants who received solutions containing benzyl alcohol. In addition, solutions containing benzyl alcohol contributed to the incidence and mortality of major intraventricular hemorrhage in low-birth-weight infants	Solutions containing benzyl alcohol should be avoided in low-birth-weight infants. A minimum amount of benzyl alcohol at which toxicity occurs has not yet been established
Phenothiazine drug class (e.g., promethazine)	A risk of severe respiratory depression has been reported in this class of drugs	Avoid the use of phenothiazines in neonates, infants, and young children
Nonprescription cough and cold products	Risk of unintentional overdose in pediatric patients when using combination , nonprescription drug products	Avoid nonprescription combination cough and cold medications in neonates, infants, and young children

PMA = postmenstrual age.

IV. PHARMACOGENOMICS

A. PG considerations alter the patient's sensitivity to certain drugs. Therefore, an understanding of the PG differences in children will increase the efficacy of some drugs while reducing the toxicity of others.

B. Definitions:
   1. Genotype: Representation of a gene
   2. Mutation: A spontaneous alteration in gene makeup. A mutation may or may not result in a change in gene function.
   3. Ontogeny: The development course of an individual from fertilization to maturity
   4. Phenotype: The expression of a genotype; the characteristic or physical counterpart of the gene function
   5. Polymorphisms: The changes or mutations that may naturally occur in genes

C. When two patients receive similar doses of a drug, there is a variability in the action and disposition of the drug. The variability is caused by many factors such as:
   1. Growth, development, and maturation state of patient
   2. Patient's diet
   3. Patient's environment
   4. Concurrent medications
   5. Other disease states
   6. Genetic makeup

D. PG Drug Dosing Considerations:
   1. Use of genotype and phenotype information to individualize therapy may optimize patient outcomes.
   2. For PG considerations in pediatric patients, the impact of ontogeny must be considered (developmental PG).

3. Most PG information has been generated from adult patients; therefore, the impact of ontogeny on the genotype-phenotype relationship has not been largely explored in children, but similar qualitative impacts are expected.

E. Identifying patients by genotype or phenotype can distinguish individuals who are at a higher risk of severe reactions associated with the drugs listed below. The metabolic enzymes associated with the following drugs alter their toxicity (drugs with warnings in labeling by the U.S. Food and Drug Administration [FDA]).
   1. Mercaptopurine – Patients with reduced TPMT (thiopurine *S*-methyltransferase) enzyme activity are more likely to experience toxicity such as neutropenia from mercaptopurine during treatment.
   2. Fluorouracil – Fluorouracil is especially toxic in patients lacking dihydropyrimidine dehydrogenase enzyme activity.
   3. Efavirenz – Infants and children with CYP2B6 poor metabolizer genotype have increased drug concentrations and toxicity.
   4. Abacavir – HLA-B polymorphism can identify subjects at risk of hypersensitivity reaction.
   5. Carbamazepine – HLA-B polymorphism can identify subjects at risk of severe rash.
   6. Phenytoin – HLA-B polymorphism can identify subjects at risk of severe rash, and those with CYP2C9 IM or poor metabolizer status can use 25% and 50% dose reductions, respectively.
   7. Irinotecan – Polymorphisms in the UGT1A1 gene are related to the gastrointestinal (GI) toxicity seen.
   8. Proton pump inhibitors – Children with CYP2C19 poor metabolizer genotype have higher drug concentrations and better clinical outcomes.
   9. Codeine – Prodrug codeine, when ingested, is converted to morphine by CYP2D6 found in the liver.
      a. Genetic variations cause some patients to metabolize some drugs more slowly (poor metabolizers) and others more rapidly (ultra-rapid metabolizers).
      b. Poor metabolizers do not experience substantial pain relief with codeine because of low conversion to morphine.
      c. The risk of opioid toxicity occurs when excessive amounts of morphine appear in the blood of ultra-rapid metabolizers.
      d. The FDA has issued a warning regarding the use of codeine in children after a tonsillectomy and/or adenoidectomy.

F. PG may directly select patients likely to respond to a medication. This is becoming more common in the development of cancer therapies where tumor mutations may be used to select potential drugs. Another example of genetic-directed therapy is the use of ivacaftor (Kalydeco or VX-770) in patients with cystic fibrosis having the G551D mutation genotype.

V. APPLIED PHARMACOKINETICS, PHARMACODYNAMICS, AND PHARMACOGENOMICS

A. Routes of Administration:
   1. Routes of administration of medications for pediatric patients are determined by the property of the drugs and the therapeutic objectives in any given patient. The routes of administration of medications are classified by delivery location.
   2. Enteral – Oral: The simplest and most common way of delivering medications
      a. Absorption: Variable and affected by many factors
      b. Advantages: Safe, most common, convenient
      c. Disadvantages:
         i. Limited absorption
         ii. Patient adherence
         iii. Different foods may affect absorption differently.

iv. Drugs may be metabolized before systemic absorption.
v. Inaccurate measurement and delivery
vi. Palatability
vii. Patient might be unable to swallow solid dosage forms.
viii. Loss of drugs during administration process
ix. Questionable stability if flavoring is used

3. Enteral – Feeding tube: Medications are delivered into the stomach (e.g., nasogastric, gastric, gastrostomy) or small bowel (nasoduodenal, nasojejunal, gastric-jejunal, jejunal) through a tube that is passed through the nasopharynx and esophagus or surgically placed.
   a. Absorption: Placement and size of tube must be considered.
      i. Most drugs are absorbed in the small intestine or stomach. If the tube is placed in the small bowel, some drugs may have minimal clinical effect if the absorption did not occur because the stomach was bypassed (e.g., antacids, sucralfate, bismuth).
      ii. Drugs undergoing extensive first-pass metabolism that are administered directly to the jejunum can result in greater absorption and systemic effect (e.g., opioids, tricyclic antidepressants).
      iii. Small-bore tubes (5–12F catheter), typically placed in the stomach or small bowel, have a greater likelihood of becoming clogged.
   b. Advantages: Can be used for both medications and enteral nutrition
   c. Disadvantages:
      i. Discomfort
      ii. Slow-release or enteric-coated medications may have inconsistent absorption.
      iii. Obstruction of the nasogastric tube
      iv. Drug binding to inside of tube
      v. Drug-food interactions must be considered, especially with enteral nutrition.
      vi. Medications can be removed if the patient is undergoing gastric suctioning.
4. Enteral – Sublingual: Administration of drug "under the tongue"
   a. Absorption: Drug-dependent
   b. Advantages:
      i. Can bypass first-pass metabolism
      ii. Can bypass destruction by stomach acid
   c. Disadvantages: Difficult to administer in a pediatric patient because of inadvertent chewing or swallowing
5. Parenteral – Intravenous: Administration of drugs or fluids directly into vein
   a. Absorption: Immediate drug exposure, given that there is no delay because of drug absorption
   b. Advantages:
      i. Most common parenteral route
      ii. Immediate systemic effect
      iii. Maximum degree of control over the circulating concentrations of the drugs
   c. Disadvantages:
      i. Bolus may result in adverse effects.
      ii. Difficulty in gaining intravenous access in small patients
      iii. Drug compatibility if administered through the same site
      iv. Selection of appropriate diluents or preservatives
      v. Volume limitations
      vi. Risk of infection or other administration reaction
      vii. Discomfort
6. Parenteral – Intramuscular: Injection of medications into muscle tissue (e.g., deltoid, vastus lateralis, ventrogluteal, dorsogluteal)

a. Absorption: Variable in premature neonates and infants because of differences in muscle mass, poor perfusion to muscles, peripheral vasomotor instability, capillary density, and insufficient muscular contractions; aqueous solutions provide rapid absorption, and depo-solutions provide slow absorption
b. Advantages:
    i. Bypasses first-pass effect
    ii. Can be given quickly in an emergency
    iii. Useful when only one medication is needed (e.g., vaccines)
c. Disadvantages:
    i. Volume limitations in pediatric patients
    ii. Discomfort

7. Parenteral – Subcutaneous: Injection into the fat layer between the skin and the muscle
    a. Absorption: Requires absorption by simple diffusion
    b. Advantages:
        i. Bypasses first-pass effect
        ii. Useful in emergencies
        iii. Useful when only one medication is needed (e.g., vaccines)
    c. Disadvantages:
        i. Discomfort
        ii. Volume limitations
8. Topical – Application of drug on the surface of the skin to treat dermatologic disorders
    a. Absorption: May be greater in neonates because of decreased skin thickness, increased skin hydration, and increased surface area/body weight ratio
    b. Advantages:
        i. Can be applied to obtain a local effect
        ii. Can be used for pain management during a procedure or injection
    c. Disadvantages:
        i. Varied absorption rates, especially in preterm and term neonates
        ii. Local reactions
        iii. Difficult to administer precise dosage amounts
9. Transdermal – Controlled delivery: Delivery of drug through the skin for systemic effects
    a. Absorption: Slow and sustained.
    b. Advantages:
        i. Bypasses first-pass effect
        ii. Painless
        iii. May minimize multiple-daily dosing regimens
        iv. May minimize adverse effects
    c. Disadvantages:
        i. Limited product availability for pediatric patients
        ii. Adult transdermal applications may cause risk to pediatric patients if used incorrectly.
        iii. Must remove prior patch when or before dosing interval is complete
10. Inhalation – Pulmonary: Delivery of drug by the lung through inhalation
    a. Absorption: Rapid delivery of drug across respiratory tract and pulmonary epithelium
    b. Advantages:
        i. Useful for gases and aerosols
        ii. Convenient for patient with respiratory issues
        iii. Delivery straight to site of action
        iv. Minimizes dose-related adverse effects

c. Disadvantages:
    i. Requires patient/caregiver education and training
    ii. Can be difficult to administer
    iii. Relies on patient adherence
    iv. Many devices were intended for adult use.

11. Inhalation – Nasal: Delivery of drug by the nasal passages through nasal inhalation
    a. Absorption: Rapid delivery of drug to the site of action
    b. Advantages:
        i. Delivery straight to site of action
        ii. Minimizes dose-related adverse effects
    c. Disadvantages:
        i. Requires patient/caregiver education and training
        ii. Difficult to administer
        iii. May cause sneezing, runny nose, and rarely epistaxis
        iv. Relies on patient administration technique
        v. Many devices were intended for adult use and do not fit neonates or small infants.
12. Rectal: Delivery of drug through the rectum for either local or systemic effect
    a. Absorption: Passive diffusion through a small surface area with an increased density of capillaries that results inerratic and incomplete absorption
        i. Rectal absorption may be increased because of the immaturity of hepatic metabolism for neonates and very young infants.
        ii. Rectal absorption may be decreased in neonates and infants because of the greater number of high-amplitude pulsatile contractions in the rectum.
    b. Advantages:
        i. Useful if patient is unwilling (e.g., infant refusal) or unable to tolerate oral options (e.g., vomiting, seizing, or unconscious)
        ii. Useful if drug is liable to degradation in the GI tract
        iii. Partial avoidance of first-pass metabolism
    c. Disadvantages:
        i. Limited by dosage forms
        ii. Discomfort
        iii. Poor patient adherence if long-term therapy
13. Intraosseous – Access through non-collapsible veins in the medullary sinuses in the bone marrow of long bones. The most common site is the proximal tibia; however, alternative sites may be used (e.g., distal tibia, distal femur, sternum, humerus).
    a. Absorption: Rapid, comparable with intravenous administration for drugs used in cardiopulmonary resuscitation situations
    b. Advantages:
        i. Allows for rapid, high-volume infusions
        ii. Useful after failed attempts for intravenous access in acute situations
        iii. Veins are supported by the bony matrix and do not collapse with hypovolemia or shock.
    c. Disadvantages:
        i. Not used for patients with cellulitis, burns, osteomyelitis, or bone fragility
        ii. Complications have included bone fracture, fat and bone marrow emboli
        iii. Drug compatibility if administered through the same site
        iv. Selection of appropriate diluent or preservative
        v. Risk of infection or other administration reaction
        vi. Discomfort

B. Pediatric-Specific Adverse Drug Reactions (ADRs) (Table 6):
   1. ADRs are defined as an unintended consequence from a drug that is noxious when used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function.
   2. PG has much to offer in enhancing drug safety, especially in populations at highest risk of ADRs.
   3. Risk factors for ADRs in children
      a. History of ADRs
      b. Extremes of age
      c. Impairment of drug clearance
      d. Polypharmacy
      e. Female sex
      f. Higher drug dose
      g. Certain genetic polymorphisms

VI. AGE-ASSOCIATED DIFFERENCES IN PATHOPHYSIOLOGY AND DISEASE

A. This section addresses examples of disease in which age is a factor in the pathophysiology of the disease.

B. Respiratory Distress Syndrome (RDS)
   1. In healthy neonates, the alveoli are coated with surfactant.
   2. In premature neonates, the surfactant may not be produced, making the neonate unable to fully open lungs and breathe.
   3. RDS treatment involves administration of surfactant.

C. Apnea
   1. Apnea in premature neonates is centrally mediated, therefore requiring treatment with methylxanthines (i.e., theophylline or caffeine).
   2. Apnea in adults is typically obstructive or mixed in origin, therefore requiring different treatments.

D. Acne
   1. Acne associated with pubertal changes is related to an increase in the activity of sebaceous glands of the skin, including the production of sebum and skin cells plugging the gland duct, resulting in inflammation and lesion formation with eventual bacterial colonization and worsening of the lesion.
   2. Adult acne may be more commonly associated with an external presentation of systemic disease.

Patient Cases

5. L.A. is a 12-year-old girl (weight 40 kg) with polycystic kidney disease receiving 4-hour hemodialysis three times weekly. Her most recent SCr is 5.0 mg/dL. Vancomycin is initiated for a MRSA infection with 600 mg given 2 hours after hemodialysis. Which best characterizes the vancomycin dosing she will need?
   A. She will need intermittent vancomycin dosing, likely twice weekly or less, and her dosing should be guided by vancomycin drug concentrations because it is difficult to determine the exact dose in advance.
   B. She should receive a standard dose of vancomycin after each dialysis session because hemodialysis removes most of the vancomycin in her body.
   C. All of her vancomycin should be administered during dialysis to minimize her risk of red man syndrome.
   D. Her vancomycin clearance can be determined on the basis of her SCr and the Schwartz equation. Serum vancomycin concentrations can be measured to fine-tune dosing when at steady state in 1–2 days.

Patient Cases *(continued)*

6. M.C. is an 8-year-old boy (weight 30 kg) who is initiated on phenytoin after a head injury. After 1 week of therapy, his initial steady-state phenytoin concentration is 22 mg/L on an oral dose of 100 mg once daily. He has had no seizures, but he is experiencing nystagmus. His dose is reduced to 50 mg once daily. Which is the most likely result of this dosage change?
   A. His phenytoin concentration will decrease but by less than the dose reduction (50%) because the current concentration is higher than the typical K_m value of 4 mcg/mL.
   B. His phenytoin concentration will stay the same because phenytoin is an auto-inhibitor, and its clearance decreases with time.
   C. His high initial phenytoin concentration for his dose suggests that he has a CYP2C9 poor or intermediate metabolizer genotype.
   D. His high phenytoin concentration is likely a result of transient protein binding changes seen in patients with head injury. Although he will need a dose reduction for now, he will need to resume a higher phenytoin maintenance dose once he is past the critical phase.

7. D.R. is a 6-year-old boy (weight 19 kg) with cystic fibrosis. His SCr is 0.4 mg/dL. He has grown *Pseudomonas aeruginosa* (minimum inhibitory concentration [MIC] 0.5 mcg/mL) from his sputum and is initiated on ceftazidime and tobramycin 120 mg every 12 hours (infused over 1 hour). He receives his doses at 9:00 a.m. and 9:00 p.m., and on the second day (third dose), a trough obtained at 8:00 a.m. is 0.5 mcg/mL and a level obtained at noon (2.0 hours after end of infusion) is 8.0 mcg/mL. Which best depicts the steady-state peak/MIC ratio in this patient?
   A. 32.
   B. 20.
   C. 16.
   D. Cannot determine from the information provided.

8. W.M. is a 3-day-old boy (height 0.39 inches, weight 1000 g) born at 26 weeks' gestation. His SCr is 1.4 and blood urea nitrogen is 39 mg/dL. He is given a single dose of vancomycin 15 mg intravenously. Assuming a vancomycin Vd of 0.6 L/kg, if his first vancomycin level obtained 24 hours post-dose is 6.25 mcg/mL, which best depicts the half-life?
   A. 4 hours.
   B. 6 hours.
   C. 8 hours.
   D. 12 hours.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Answer B is correct because it is highly protein bound. Phenytoin does not displace bilirubin and can be used as anticonvulsant therapy in newborns (Answer A is incorrect). However, this high binding and the low albumin concentrations in newborns result in a higher free fraction in newborns, which needs to be considered when interpreting phenytoin concentrations in infants. Phenobarbital can induce phenytoin metabolism and can require larger phenytoin doses (Answer C is incorrect). Some *HLA* genotypes have been associated with the development of rash (not hepatotoxicity), but this is a rare adverse event in newborns (Answer D is incorrect).

2. Answer: B

Answer B is correct because the high renal clearance and short half-life of vancomycin in pediatric patients require more frequent dosing than in adults (Answer D is incorrect). Although it is true that renal function matures to an "adult level" by 2 years of age, this is when clearance is normalized by BSA (liters per hour per 1.73 square meters). Clearance normalized by weight (liters per hour per kilogram) is higher in young children than in adults. Very little vancomycin is hepatically metabolized (Answer A is incorrect). Although there is some binding to plasma proteins, it is less than 50%, and changes in binding need not be considered (Answer C is incorrect).

3. Answer: B

Answer B is correct because valproate has saturable protein binding, which competes with phenytoin for binding on albumin, leading to a higher phenytoin free fraction. Valproate is associated with greater hepatotoxicity in young children than in adults (Answer A is incorrect). It does not induce CYP enzymes but is an inhibitor of glucuronidation (Answer C is incorrect). It is not a substrate for CYP2D6; thus, a patient's *CYP2D6* genotype has no influence on valproate PK (Answer D is incorrect).

4. Answer: C

Answer C is correct because the concentration 6 hours after the second dose can be calculated as 5.7 mcg/mL using superpositioning (Answer D is incorrect). Given the two concentrations after the first dose, the half-life and terminal rate constant can be determined. In this case, the reduction of 75% from 7.2 to 1.8 indicates that 2 half-lives have passed during the 12-hour interval (6 and 18 hours after the first dose). Thus, the half-life is 6 hours. The contribution of the first dose to the level after the second dose is the level just before the second dose, 1.8 mcg/mL, decayed for 6 hours or 1 half-life to 0.9 mcg/mL. The contribution of the second dose to the level 6 hours post-dose number 2 is the ratio of the dose (2)/dose (1), (10 mg/15 mg), times the concentration seen 6 hours after dose 1. This is 0.67 x 7.2 mcg/mL, or 4.8 mcg/mL. The combined contribution of the two doses results in a concentration of 4.8 + 0.9, or 5.7 mcg/mL, 6 hours after the second dose, not 7.2 or 9.0 mcg/mL (Answers A and B are incorrect).

5. Answer: A

Answer A is correct because vancomycin is almost exclusively eliminated renally, and only a limited amount is removed during a standard hemodialysis session (Answer B is incorrect). Thus, supplementation with every dialysis is usually unnecessary. The amount removed by dialysis is increased if vancomycin is administered during dialysis because of the higher plasma concentrations during vancomycin's distributive phase. However, red man syndrome can best be avoided by reducing the infusion rate, not by administration during dialysis (Answer C is incorrect). Because dialysis removes SCr, SCr in dialysis patients cannot be used to quantify residual renal function (Answer D is incorrect).

6. Answer: C

Answer C is correct because phenytoin is metabolized primarily by CYP2C9, and genetic polymorphisms of this enzyme are associated with different dosing requirements. Phenytoin has significant nonlinear metabolism in the therapeutic range. Thus, changes in phenytoin dosage result in larger than proportional changes in phenytoin concentrations (Answer A is incorrect). Phenytoin is an inducer, not an inhibitor, of drug metabolism (Answer B is incorrect). Its nonlinear metabolism makes it difficult to see metabolism induction changes over time. However, increasing phenytoin doses to maintain stable phenytoin concentrations are often required in patients with closed head injury. Patients with head injury also often experience reductions in albumin concentrations, altering the phenytoin free fraction. However, this results in lower, not higher, total phenytoin concentrations (Answer D is incorrect).

7. Answer: A

Answer A is correct because at steady state, the peak/MIC ratio is 32. The half-life can be determined from any two concentrations after a single dose or around any dose at steady state (Answer D is incorrect). Because the 2-hour post-end of the infusion (C2) concentration is 8 mcg/mL and the C10 is 0.5 mcg/mL, 4 half-lives have transpired between those two collection times of 8 hours (0.5 mcg/mL is 1/16 or 0.067 of 8.0 mcg/mL). Thus, the half-life is 8 hours/4 or 2 hours. The peak concentration at the end of the infusion is 2 hours (1 half-life) before the C2, so the peak is double the C2 of 8 mcg/mL, or 16 mcg/mL. With a given MIC of 0.5 mcg/mL, the peak/MIC is 32, not 20 or 16 (Answers B and C are incorrect).

8. Answer: D

Answer D is correct because the half-life is 12 hours given PK calculations with the provided PK parameters and drug concentrations. With a Vd of 0.6 L/kg and a weight of 1 kg, this patient's Vd is 0.6 L. Because Cmax = dose/Vd, the 15-mg dose would be expected to produce a Cmax of 15/0.6 or 25 mcg/mL. The vancomycin concentration obtained 24 hours later is 6.25 or 25% of the Cmax. This means that 2 half-lives have transpired over 24 hours; thus, the half-life is 24/2 or 12 hours, not 4, 6, or 8 hours (Answers A–C are incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

Answer A is correct because the primary CYP3A isoform at birth is CYP3A7. Because CYP3A7 is present at birth, Answer B is incorrect. It is replaced in the first month of life by CYP3A4 (Answer D is incorrect). Very little CYP3A7 is found in the liver of adolescents and adults (Answer C is incorrect).

2. Answer: D

Answer D is correct because infants often have a different disease pathophysiology and underlying etiology that can lead to different responses to drug concentrations. Differences in skin surface area and pulmonary surface area may affect local absorption but will not change PD (Answers A and B are incorrect). Metabolic rate also does not play a role in PD drug response (Answer C is incorrect).

3. Answer: C

Answer C is correct because the volume of drug that can be administered intramuscularly is limited, which is an important limitation of this route of administration in neonates. Total body water has no impact on intramuscular drug administration (Answer A is incorrect); first-pass metabolism does not occur after intramuscular administration (Answer B is incorrect), and although neonates have lower binding proteins, this does not affect intramuscular administration (Answer D is incorrect).

4. Answer: D

Answer D is correct because infants' SCr concentrations at birth are at near equilibrium with that of their mothers. Thus, the SCr for the first few days of life is not a true reflection of infant renal function. Although nephrogenesis is active between weeks 32 and 40, more development in activity occurs postnatally than in utero (Answer A is incorrect). Although there is evidence of induction of secretion by penicillins and other agents that are eliminated by secretion, there is no evidence of this inducing the ontogeny of GFR (Answer B is incorrect). Renal development continues for many months after birth (Answer C is incorrect).

5. Answer: D

Answer D is correct because the liver/total body weight ratios are about double in infants compared with in adults. Age-related differences in receptors may vary in different age groups, but there is no consistent pattern of infants having fewer receptors or higher EC_{50} values (Answer A is incorrect). The liver CYP3A content is relatively similar in toddlers and adults (Answer B is incorrect), and toddlers have similar or increased first-pass metabolism compared with adults (Answer C is incorrect).

6. Answer: C

Answer C is correct because codeine has little direct effect on opioid receptors, but it is metabolized by CYP2D6 to morphine. Ultra-metabolizers produce more morphine. Poor metabolizers produce very little morphine from codeine and have few therapeutic effects from codeine (Answer A is incorrect). Morphine is glucuronidated, not metabolized, by CYP2D6, so the *CYP2D6* genotype has no impact on morphine PK (Answer B is incorrect). Poor CYP2D6 metabolizers produce a low amount of morphine from codeine and thus have a blunted response to codeine therapy (Answer D is incorrect).

7. Answer: A

Answer A is correct because the lower plasma protein binding results in larger Vd values in newborns. Total body water is higher, not lower, than in older populations (Answer B is incorrect). A greater portion of total body is extracellular, not intracellular, in newborns (Answer C is incorrect). Newborns do not have a high body fat content at birth (Answer D is incorrect). Term infants have limited body fat, and preterm infants have very low body fat.

8. Answer: C

Answer C is correct because reduced gastric acid secretion in neonates can lead to higher gastric pH. Some drugs require acid for neutral ionization and optimal solubility. For these drugs, absorption may be reduced in neonates. Renal gentamicin clearance is reduced in infants because of immature GFR. Gastric emptying time is increased, not decreased, in neonates (Answer A is incorrect). Transdermal absorption is greater in newborns, but it is caused by increased hydration and thinner skin (Answer B is incorrect). Although intravenous access may be limited in neonates, intramuscular absorption is not predictable (Answer D is incorrect).

9. Answer: C

Answer C is correct because infant renal function is immature compared with that of adults, resulting in lower clearance of renally eliminated drugs, including amino-

glycosides. Both Vd and clearance contribute to a longer half-life (Answer A is incorrect). As stated earlier, the Vd of aminoglycoside is increased in neonates (Answer B is incorrect). Although clearance is variable in newborns, it is consistently lower than in adults with normal renal function (Answer D is incorrect).