

PEDIATRIC PHARMACY

PREPARATORY REVIEW AND RECERTIFICATION COURSE



2022 ACCP UPDATES IN THERAPEUTICS®



AMERICAN COLLEGE OF CLINICAL PHARMACY

ACCP UPDATES IN THERAPEUTICS®:
PEDIATRIC PHARMACY PREPARATORY REVIEW
AND RECERTIFICATION COURSE

AMERICAN COLLEGE OF CLINICAL PHARMACY

UPDATES IN THERAPEUTICS[®]

**PEDIATRIC PHARMACY PREPARATORY REVIEW
AND RECERTIFICATION COURSE**

2022 EDITION



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Note: The authors and publisher of the Pediatric Pharmacy Preparatory Review and Recertification Course recognize that the development of this material offers many opportunities for error. Despite our very best efforts, some errors may persist into print. Drug dosage schedules are, we believe, accurate and in accordance with current standards. Readers are advised, however, to check other published sources to be certain that recommended dosages and contraindications are in agreement with those listed in this book. This is especially important in new, infrequently used, or highly toxic drugs.

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Errata: When possible, corrections to this publication are included in the 2022 Pediatric Pharmacy Preparatory Review and Recertification Course Errata which will be available at www.accp.com/media/pedpc22/errata.pdf.

Continuing Pharmacy Education:

The American College of Clinical Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. The Universal Activity Numbers for the Pediatric Pharmacy Preparatory Review and Recertification Home Study Course, 2022 edition are as follows: Foundation of Pediatric Pharmacy Practice: Principles, Communications, and Education, Biostatistics, Study Designs: Design and Application, Medication Safety, Activity No. 0217-0000-22-249-H04-P, 4.25 contact hours; PICU I, PICU II, Neonatology, Activity No. 0217-0000-22-250-H01-P, 4.0 contact hours; Endocrine Disorders, Pharmacokinetics, Pharmacodynamics, Pharmacogenomics, and Drug Formulations, Practice Management, Toxicology, Activity No. 0217-0000-22-251-H01-P, 4.5 contact hours; Gastroenterology, Infectious Diseases, Hematology and Oncology, Activity No. 0217-0000-22-252-H01-P, 4.0 contact hours; Solid Organ Transplantation, Cardiology, Pulmonary, Pediatric Public Health and Patient Advocacy, Activity No. 0217-0000-22-253-H01-P, 4.25 contact hours; Immunology, Nephrology, Neurology/Psychiatry, Fluids, Electrolytes, and Nutrition, Activity No. 0217-0000-22-254-H01-P, 4.25 contact hours. All Pediatric Pharmacy Preparatory Review and Recertification Course sessions are application-based activities.

To earn continuing pharmacy education credit for the 2022 Pediatric Pharmacy Preparatory Review and Recertification Course for home study, you must review all content and complete the attestation statements and course evaluations by November 29, 2025. Statements of continuing pharmacy education credit will be available at CPE monitor within 2–3 business days after completion of this activity.

Board Certified Pediatric Pharmacy Specialist (BCPPS) Recertification Credit

The Pediatric Pharmacy Preparatory Review and Recertification Course is part of a Board of Pharmacy Specialties (BPS)-approved professional development program for BCPPS recertification credit. To be eligible to earn 25.25 contact hours of pediatric pharmacy recertification credit for the 2022 Pediatric Pharmacy Preparatory Review and Recertification Course, you must purchase and successfully submit the completed web-based posttest(s) by 11:59 p.m. (CDT) on December 8, 2023. To learn more about the Board of Pharmacy Specialties (BPS) specialty exams, please visit their website: www.bpsweb.org.

The American College of Clinical Pharmacy (ACCP) has compiled the materials in this course book for pharmacists to use in preparing for the Board of Pharmacy Specialties (BPS) Pediatric Pharmacy Specialty Certification Examination. There is no intent or assurance that all of the knowledge on the examination will be covered in the ACCP process. Although ACCP does use the BPS Content Outline in creating the material for this course, ACCP does not know the specific content of any particular BPS examination. BPS guidelines prohibit any overlap of individuals writing the examination and developing preparatory materials. To maintain its strict, independent standards for certification, BPS does NOT endorse or provide review information, preparatory courses, or study guides for Board Certification Examinations.

PROGRAM GOALS AND TARGET AUDIENCE

Updates in Therapeutics®: Pediatric Pharmacy Preparatory Review and Recertification Course is designed to help pharmacists who are preparing for the Board of Pharmacy Specialties certification examination in Pediatric Pharmacy as well as those seeking a general review and refresher on disease states and therapeutics. The program goals are as follows:

1. To present a high-quality, up-to-date overview of disease states and therapeutics;
2. To provide a framework to help attendees prepare for the specialty certification examination in pediatric pharmacy; and
3. To offer participants an effective learning experience using a case-based approach with a strong focus on the thought processes needed to solve patient care problems in each therapeutic area.

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AMERICAN COLLEGE OF CLINICAL PHARMACY

ACCP UPDATES IN THERAPEUTICS®:
PEDIATRIC PHARMACY PREPARATORY REVIEW
AND RECERTIFICATION COURSE

FOUNDATION OF PEDIATRIC PHARMACY PRACTICE: PRINCIPLES, COMMUNICATIONS, AND EDUCATION

HAE JIN CHO, PHARM.D.

**THE UNIVERSITY OF NORTH TEXAS HEALTH SCIENCE CENTER
AT FORT WORTH COLLEGE OF PHARMACY
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Learning Objectives

1. Define pediatric patients and the corresponding normal limits of vital signs and laboratory values on the basis of age.
2. Compare fundamental differences between pediatric and adult patients in medication therapy management, including availability of treatment options, clinical evidence, and pediatric-friendly formulations.
3. Define off-label medication use and its implications in pediatric medication therapy.
4. Apply foundational pharmacotherapeutic concepts and pediatric-specific factors to provide care.
5. Develop rapport with patients by considering the different developmental stages of pediatric patients.
6. Integrate principles and tools to effectively communicate with patients and caregivers.
7. Identify factors influencing the need for pharmacists to be effective educators and preceptors.
8. Apply educational frameworks and evidence-based methods to design instructions for didactic and experiential learning.
9. Describe strategies to promote experiential learning such as instructing, modeling, coaching, and facilitating.
10. Apply best practices of assessment in evaluating achievement of learning outcomes.

Abbreviations in This Chapter

AAP	American Academy of Pediatrics
ABE	Ability-based education
ABO	Ability-based outcome
ACPE	Accreditation Council for Pharmacy Education
APPE	Advanced pharmacy practice experience
BMI	Body mass index
BSA	Body surface area
CPD	Continuing professional development
eHealth	Electronic health
FDAMA	Food and Drug Administration Modernization Act
IPPE	Introductory pharmacy practice experience
KIDs List	Key Potentially Inappropriate Drugs in Pediatrics List
PD	Pharmacodynamics

PGY2	Postgraduate year two
PK	Pharmacokinetics
SOAP	Subjective, objective, assessment, and plan

Self-Assessment Questions

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

1. A 1-week-old boy, previously born at 28 weeks' gestation with a birth weight of 1200 g, is in the ICU. Which is most applicable to the patient?
 - A. He is an infant.
 - B. He was born full term.
 - C. He had a very low birth weight.
 - D. He cannot perceive pain.
2. A 5-year-old girl (weight 20 kg) was prescribed lansoprazole 1.5 mg/kg orally once daily for gastroesophageal reflux disease. According to the American Academy of Pediatrics (AAP), for this indication, lansoprazole is recommended to be taken at 0.7–3 mg/kg/day (maximum daily dose 30 mg/day). She was instructed to take 3 mg/mL of simplified lansoprazole solution by measuring 30 mL to provide the prescribed dose. Which factor most likely contributed to the medication error present in this case?
 - A. Calculation errors.
 - B. Failure to recognize maximum dosing.
 - C. Lack of pediatric-friendly dosage formulations.
 - D. Use of trailing zeros
3. Which best names the regulatory change that provided the extension to the Food and Drug Administration Modernization Act (FDAMA) offering an additional 6 months of patent exclusivity for on-patent drugs being tested for pediatric use?
 - A. Pediatric Rule.
 - B. Orphan Drug Act.
 - C. Pediatric Research Equity Act.
 - D. Best Pharmaceuticals for Children Act.
4. A 16-year-old female adolescent is admitted to the pediatric ICU for diabetic ketoacidosis. Which would be most appropriate to optimize her medication therapy?

- A. Assume good medication adherence.
 - B. Use dosing references for adults.
 - C. Provide motivational interviewing.
 - D. Conceal sensitive issues such as psychosocial concerns.
5. A 5-year-old boy and his father present to the pharmacy with a new prescription for fluticasone 50 mcg nasal spray. It is written to use 1 spray in each nostril once daily. The pharmacist is asked to provide education regarding the patient's new medication. Which communication technique would be most appropriate to integrate when counseling about the child's medication?
 - A. Sit above their eye level.
 - B. Use an animated tone of voice.
 - C. Give ample time for them to respond to questions.
 - D. Maintain eye contact regardless of their cultural background.
6. A 3-year-old boy presents to urgent care with an adult caregiver. The caregiver speaks primarily Spanish and limited English. The child was prescribed a new medication for home use. A pharmacist has been consulted to provide education about the medication. Which recommendation would be most appropriate when communicating with the caregiver?
 - A. Determine who will be giving the medication to the child.
 - B. Encourage the caregiver to provide the child with full autonomy.
 - C. Provide medication information handouts written in English.
 - D. Dismiss any misconceptions or fears expressed by the caregiver..
7. Which Accreditation Council for Pharmacy Education (ACPE) standard best addresses ACPE's commitment to continuing professional development (CPD)?
 - A. Standard 6: College or School Vision, Mission, and Goals.
 - B. Standard 12: Pre-APPE Curriculum.
 - C. Standard 19: Faculty and Staff – Qualitative Factors.
 - D. Standard 20: Preceptors.
8. A pharmacist is developing an in-service training and would like to evaluate the learners' comprehension of content. According to Bloom's taxonomy, which verb would be most appropriate to use to create the learning objective?
 - A. Define.
 - B. Explain.
 - C. Prioritize.
 - D. Recommend
9. An advanced pharmacy practice experience (APPE) student begins a rotation at a pediatric medical center. The student's primary role is to optimize medication therapies for pediatric patients. As a preceptor, you would like to maximize the student's development of critical thinking skills and provide specific and constructive feedback through a more efficient and effective approach. Which case presentation model for experiential learning would be most appropriate to apply to the case?
 - A. Traditional case presentation.
 - B. One-minute preceptor.
 - C. SNAPPS model.
 - D. Think-aloud model.
10. A postgraduate year two (PGY2) pediatric pharmacy resident is on a pediatric ICU rotation. The preceptor aims to facilitate the development of the resident's self-awareness to promote greater learning gains during the rest of the rotation. Which assessment strategy would be most appropriate to apply to the case?
 - A. 360-degree assessment.
 - B. Peer assessment.
 - C. Reflective journaling.
 - D. Self-assessment.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

Domain 1: Patient Management;

- Task(s):
 - o 1.1 Collect patient-specific information on which to base safe and effective medication therapy.
 - o 1.2 Analyze and interpret collected patient information.
 - o 1.4 Design, recommend, implement, and document age and developmentally appropriate cost-effective therapeutic regimen with health care team and patient/caregivers.
 - o 1.5 Design and implement a plan to monitor the safety and efficacy of a therapeutic regimen, and adjust as necessary.
 - o 1.8 Identify and manage barriers to successful transitions of care (e.g., social barriers, prior authorization, payment considerations).

Domain 2: Practice Management and Medication Safety;

- Task(s):
 - o 2.1 Develop and implement systems to ensure appropriate drug delivery throughout the medication use process.
 - o 2.2 Collaborate in the selection, implementation, and maintenance of equipment/technology and decision support involved in the medication use process.
 - o 2.4 Adopt, adapt or develop evidence-based practice guidelines and protocols for the management of pediatric patients in accordance with health system policies and procedures.

Domain 3: Information Management, Research, and Education;

- Task(s):
 - o 3.1 Educate health care professionals, trainees, and students concerning safe and effective use of medications and other issues related to the care of the pediatric patient.
 - o 3.2 Provide medication counseling to patients/caregivers regarding the safe and effective use of medications, adverse effects, and the importance of adherence to the treatment regimen.
 - o 3.4 Retrieve and interpret biomedical literature with respect to study method, statistical analysis, study results, and applicability to pediatric pharmacy practice.

Domain 4: Public Health and Patient Advocacy;

- Task(s):
 - o 4.2 Advocate for the availability of age-appropriate formulations, safety and efficacy studies, and product labeling.
 - o 4.4 Advocate for pediatric pharmacy practice and advanced training through professional organizations.

OVERVIEW

The purpose of this review is to reinforce the foundations of pediatric patient care and enhance the abilities of pediatric pharmacists as educators and preceptors.

I. PRINCIPLES OF PEDIATRICS

Pediatric patients are not simply “small adults” – they are their own population with a need for specialized patient care (N Engl J Med 2003;349:1157-67). This section provides an overview of pediatric pharmacy practice, focusing on the provision of safe and effective medication therapy in the pediatric population.

A. Epidemiology of the U.S. Pediatric Population

1. The pediatric population accounts for almost 25% of the U.S. population. The State of America’s Children 2021 report from the Children’s Defense Fund stated that 22% of the U.S. population was composed of children in 2019 (Children’s Defense Fund 2021).
 - a. Around 13.8 million pediatric patients in the United States have special health care needs, which include children and youth who have chronic conditions, medically complex health issues, and/or behavioral or emotional conditions as defined by the Maternal and Child Health Bureau (AMCHP 2022).
 - b. In pediatric patients, the medication-related problems for which they have been prescribed and taken medication regularly for at least 3 months increase with age, occurring in around 5.6% at 0–4 years, 11.4% at 5–11 years, and 17.7% at 12–17 years (NCHS Summary Health Statistics 2018).
2. Pediatric patients account for a considerable proportion of patients receiving health care, including in community pharmacies, ambulatory clinics, EDs, and hospitals.
 - a. In 2018, there were around 180 visits per 100 people per year in the ambulatory care setting among patients younger than 15 years, which is substantial relative to the 267 visits per 100 people per year that included all ages (NCHS National Ambulatory Medical Care Survey 2018).
 - b. In addition, more than 30 million ED visits occurred among pediatric patients younger than 15 years, which made up around 20% of all visits in 2019 (CDC 2022).

B. Role of a Pediatric Pharmacist

1. Pharmacists who care for pediatric patients should be knowledgeable about disease states and medication therapy and have the skills to apply the knowledge to practice. Their responsibilities include, but are not limited to (Pharmacotherapy: Principles and Practice 2016:19-29):
 - a. Medication selection and use
 - b. Monitoring of effectiveness and toxicity
 - c. Prevention of medication errors
 - d. Patient and caregiver education
 - e. Contributions to knowledge through research
2. Several professional organizations support the pharmacist’s role in pediatric patient care, including:
 - a. American College of Clinical Pharmacy (Pharmacotherapy 2005;25:1277-82)
 - b. American Society of Health-System Pharmacists (Am J Hosp Pharm 1991;48:2475-7; Am J Hosp Pharm 1994;51:1690-2; ASHP/PPAG 2016)
 - c. Pediatric Pharmacy Association (J Pediatr Pharmacol Ther 2011;16:118-22; PPA Position Statements)
 - d. American Academy of Pediatrics (AAP) (Pediatrics 2003;112:431-6)
3. In 2022, there are 74 postgraduate year two (PGY2) pediatric pharmacy residency programs, 65 of which have obtained full accreditation status from the American Society of Health-System Pharmacists (ASHP Online Residency Directory).

4. Since 2015, the Board of Pharmacy Specialties has administered the Pediatric Pharmacy Certification examination for pharmacists to become Board Certified Pediatric Pharmacy Specialists (BPS Pediatric Pharmacy).

C. Classification of Pediatric Patients

1. Pediatric patients are often classified on the basis of age, expressed in days, weeks, months, or years. Table 1 defines common age terms in children. Some government agencies combine adolescents with young adults who are up to 24 years of age (FDA Guidance for Industry, E11; J Adolesc Health 2009;45:8-24; N Engl J Med 2003;349:1157-67; Pediatrics 2004;114:1362-4).
2. Additional classifications are based on other factors such as birth weight and gestational age as described in Table 1.
3. The classification of pediatric patients is an important guide to medication selection and dosing because medications can be affected or contraindicated in some patients depending on their age or development of organ function (e.g., kidney, liver). For example, elixir formulations should be avoided, when possible, in neonates and infants, because at such ages, pediatric patients lack the ability to effectively metabolize alcohol by alcohol dehydrogenase, whereas adults have this ability (Fundam Clin Pharmacol 2003;17:281-99; J Adolesc Health 2009;45:8-24).

Table 1. Pediatric Age Classification and Definitions

Common Age Classification	
Neonate	Age $\leq$ 28 days
Infant	Age 29 days to $\leq$ 12 mo
Child	Age $>$ 12 mo to 12 yr
Adolescent	Age 13–17 yr (some use definition up to 21 yr)
Neonatal Terminology	
Gestational age (GA)	Age from date of mother's first day of last menstrual period to date of birth
Full term	Born at $\geq$ 37 wk gestation
Premature	Born at $<$ 37 wk gestation
Chronological (postnatal) age	Age from birth to present, measured in days, weeks, months, or years
Corrected (adjusted) age	May be used to describe age of a premature child $\leq$ 3 yr: Corrected age: = Chronological age in months – [(40 – GA at birth in week) $\times$ 1 mo $\div$ 4 wk]
Neonatal Weight Classification	
Low birth weight	Premature infant with birth weight of 1500–2500 g
Very low birth weight	Premature infant with birth weight 1000 g to $<$ 1500 g
Extremely low birth weight	Premature infant with birth weight $<$ 1000 g
Small for gestational age (SGA)	Birth weight $<$ 10th percentile among neonates of the same GA
Large for gestational age (LGA)	Birth weight $>$ 90th percentile among neonates of the same GA

Information from: FDA Guidance for Industry, E11; J Adolesc Health 2009;45:8-24; N Engl J Med 2003;349:1157-67; Pediatrics 2004;114:1362-4.

D. Growth and Development

1. Infants and children are often monitored for their growth.
 - a. Markers of physical growth include:
 - i. Weight
 - ii. Length or height
 - iii. Head circumference
 - iv. Weight-for-length
 - v. Body mass index (BMI)
 - b. These markers are age- and sex-dependent; therefore, using the correct tools for measuring pertinent variables on the basis of these factors is important to assess the nutritional status and physical growth of pediatric patients.
 - i. For infants and children younger than 2 years, the WHO growth charts are recommended for assessment (WHO Growth Charts).
 - ii. The WHO growth charts reflect growth according to the standard for infant feeding, represented by infants who were predominantly breastfed for at least 4 months, which was continued through 12 months of age.
 - iii. For children 2 years and older, the CDC growth charts are recommended for assessment (CDC Growth Charts).
2. Motor development milestones are monitored closely, especially during the first 2 years of life. Motor skills can be divided into two classifications.
 - a. Gross motor skills are often considered large movement. Examples include holding the head steady while upright, sitting upright on one's own, beginning to walk, beginning to run, and beginning to jump at ages 2, 6, 12, 18, and 24 months, respectively (Nelson Textbook of Pediatrics 2020:22;131-7.e1, 2020:23;137-143.e1).
 - b. Fine motor skills are considered smaller movements. 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, assessed for the time intervals similar to those for gross motor skills (Nelson Textbook of Pediatrics 2020:22;131-7.e1, 2020:23;137-143.e1; Pediatrics 2006;118:405-20).
 - c. These markers of normal physical development 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.
3. Piaget's classification of cognitive development is discussed in greater detail in the Communications with Pediatric Patients and Caregivers section.
4. Assessments of growth, motor, and cognitive developmental milestones are recommended during each pediatric preventive care visit, also known as a well-child visit. These visits occur more often early in life (i.e., every 1–2 months in infancy) and then annually. These well-child visits allow (Pediatrics 2016;137:26-7):
 - a. Detection of developmental delay as early as possible
 - b. Provision of preventive care, including routine childhood immunizations
 - c. Opportunity for caregivers to raise any concerns they may have and to engage in the child's health

E. Differences in Pediatric Patient Data – Vital Signs, Laboratory Values, and Calculations

1. Vital Signs: Assessment of vital signs, as in adult medicine, is imperative in the evaluation of pediatric patients. Changes in vital signs can indicate effectiveness and safety in medication therapy. Normal values for blood pressure, heart rate, respiratory rate, and body temperature differ from adult values because of physiologic differences and are age-dependent.

- a. Blood pressure ranges depend on age, sex, and height percentile.
 - i. The AAP guidelines provide blood pressure reference ranges for assessment on the basis of age, sex, and height for children 1 year and older.
 - ii. In general, the ranges of systolic blood pressure at the 50th percentile can be as follows:
 - (a) Children 1–5 years: 80–98 mm Hg
 - (b) Children 6–11 years: 91–106 mm Hg
 - (c) Children and adolescents 12–17 years: 99–122 mm Hg
 - (d) For specific ranges based on height percentile, sex, and age, see 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).
 - iii. In general, blood pressure trends upward with increasing age.
- b. Heart and respiratory rate ranges can vary by resource and are not necessarily evidence based (Lancet 2011;377:1011-8).
 - i. In general, heart rate trends downward with increasing age (AHA 2006).
 - (a) Birth up to 3 months of age: 85–205 beats/minute
 - (b) At 2 years: 100–190 beats/minute
 - (c) Children 2–10 years: 80–140 beats/minute
 - (d) Children and adolescents older than 10 years: 60–100 beats/minute, closer to the heart rate range of adults
 - ii. Respiratory rate, similar to heart rate, trends downward with increasing age (AHA 2006).
 - (a) Infants: 30–60 breaths/minute
 - (b) Children up to 3 years: 24–40 breaths/minute
 - (c) Children 3–5 years: 22–34 breaths/minute
 - (d) School-aged children up to about 12 years: 18–30 breaths/minute
 - (e) Adolescents: 12–16 breaths/minute, approaching adult values
- c. Body temperature can be determined by the rectal, oral, axillary, and tympanic routes.
 - i. The range of normal body temperature may differ depending on the route of measurement (Paediatr Child Health 2000;5:273-84):
 - (a) Rectal: 36.6°C–38°C (97.9°F–100.4°F)
 - (b) Oral: 35.5°C–37.5°C (95.9°F–99.5°F)
 - (c) Axillary: 34.7°C–37.3°C (94.5°F–99.1°F)
 - (d) Tympanic: 35.8°C–38°C (96.4°F–100.4°F)
 - ii. The preferred method of measuring body temperature varies depending on patient age.
 - (a) Rectal temperature measurement is recommended by the AAP for children younger than 4 years.
 - (b) For older children, oral measurement can be used.
 - (c) Axillary measurement can be used for patients as young as 3 months, though it is thought to be less accurate than oral and rectal measurements.
 - (d) Tympanic measurement is considered potentially less accurate because of cerumen accumulation (Acad Emerg Med 1995;2:17-9; AAP 2020).
 - (e) Some institutions use temporal artery thermometry, which is most accurate in patients older than 3 months (Arch Pediatr Adolesc Med 2001;155:376-81).
 - iii. Fever is a normal physiologic response involving the hypothalamic reaction to pyrogens, and its presence should not be the cause for immediate medication therapy in otherwise healthy pediatric patients unless it is accompanied by discomfort. Patients at increased risk of severe infection should be evaluated further.
 - (a) In general, temperature ranges are as follows:
 - (1) Mean normal temperature: 98.6°F (37°C)

- (2) Low-grade fever: temperature 100°F–102°F (37.8°C–39°C).
 - (3) High fever: temperature greater than 104°F (40°C)
- (b) Antipyretics such as acetaminophen may be given for body temperatures greater than 101°F (38.3°C), measured by any route, if the patient presents with discomfort (Pediatrics 2011;127:580-7).
- (c) The definition of fever can vary depending on route of measurement and patient age.
- d. Pain scores are an important marker and should be part of the routine assessments of pediatric patients. Pain is perceived by patients of all ages, including newborns.
 - i. Standardized pain assessment scale
 - (a) In neonates or infants: Neonatal Infant Pain Scale (NIPS) (Neonatal Netw 1993;12:59-66)
 - (b) Children up to age 4 years: Face, Legs, Activity, Cry, Consolability (FLACC) (Pediatr Nurs 1997;3:293-7)
 - (c) In children older than 4 years: the Wong-Baker FACES scale, with graphic facial expressions (Wong's Essentials 2005)
 - (d) In older children who can verbalize and comprehend number values: A visual analog scale or a numeric pain scale
 - ii. In patients with limited ability to have direct communication, such as neonates, infants, and young children and some older pediatric patients (e.g., critically ill individuals) who may be unable to verbally express pain symptoms, indicators of pain include physiologic markers, such as increased respiratory and/or heart rate and oxygen desaturations, as well as changes in behavior (e.g., grimacing or high-pitched crying).
- 2. Laboratory Values: Normal laboratory values in infants and children can differ from those in adults. Physiologic differences account for variation in normal ranges by age.
 - a. With the advances in software technology, laboratories now often report abnormal values with adjacent normal ranges according to the age of pediatric patients.
 - b. Standard pediatric handbooks or references such as *The Harriet Lane Handbook* (2021) and the *Pediatric & Neonatal Dosage Handbook* (2021) also serve as resources for normal laboratory values for pediatric patients.
- 3. Calculations: Calculations used to assess pediatric patients differ from those used to assess adult patients.
 - a. The body surface area (BSA), BMI, and ideal body weight calculations described in Table 2 are sometimes used in the dosing of certain medications and in the assessment of nutritional status (Am J Clin Nutr 2002;75:978-85; Am J Hosp Pharm 1983;40:107-10; N Engl J Med 1987;317:1098).
 - b. Creatinine clearance is used to assess a patient's renal function and is applied in dosing to prevent accumulation of the medication (e.g., when renal dysfunction is present or the patient is taking a potentially nephrotoxic drug).
 - i. The Cockcroft-Gault and Jelliffe equations have been studied and validated in healthy adult populations but should not be applied when evaluating pediatric patients (Ann Intern Med 1973;79:604-5; Nephron 1976;16:31-41).
 - ii. The Schwartz equation is used to calculate estimated creatinine clearance in pediatric patients, including low-birth-weight infants and patients up to age 21 years (Pediatr Clin North Am 1987;34:571-90; Pediatr Nephrol 2010;25:2321-6).
 Limitations: The Schwartz equation can potentially overestimate glomerular filtration rate (GFR), especially in moderate to severe renal insufficiency, because serum creatinine is a crude marker of GFR (Pediatr Nephrol 1996;10:709-11; Pediatr Nephrol 2010;25:2321-6).
 - iii. The bedside Schwartz equation is a modified Schwartz equation for patients 1–18 years of age and is the recommended equation for estimating GFR in children according to the National Kidney Foundation (NKF 2009).

- iv. Cystatin C or BUN has been proposed to estimate GFR in children with renal insufficiency such as chronic kidney disease (J Am Soc Nephrol 2009;20:629-37; Pediatr Nephrol 2003;18:981-5).
- v. Most equations in Table 2 apply to infants, children, and adolescents; however, application of these equations is limited in the neonatal population.

Table 2. Common Equations Used for Data Calculations in Pediatric Patients

Calculation	Equation
Body surface area (BSA) ^a	$BSA (m^2) = \text{square root} [(height \times weight) \div 3600]$
Body mass index (BMI) ^a	$BMI = weight \div height \div height \times 10,000$
Ideal body weight (IBW) ^a	$IBW (kg) = [(height)^2 \times 1.65] \div 1000$
CrCl or estimated GFR	Original Schwartz Equation $CrCl (mL/minute/1.73 m^2) = [k \times L] \div SCr$ k = proportionality constant L = length in centimeters SCr = serum creatinine in mg/dL Premature infant age ≤ 1 yr: k = 0.33 Term infant age ≤ 1 yr: k = 0.45 Child (male or female) or adolescent female: k = 0.55 Male adolescent: k = 0.7 Bedside Schwartz Equation (Modified Schwartz Equation) for patients age 1–18 yr $CrCl = [0.413 \times L] \div SCr$
Estimation of pediatric dosing when limited pediatric-dosing data are available	Approximate pediatric dose = adult dose $\times [BSA (m^2) \div 1.73 m^2]$

^aHeight in centimeters, weight in kilograms.

Information from: Am J Clin Nutr 2002;75:978-85; Am J Hosp Pharm 1983;40:107-10; JAMA 1965;193:443-6; J Am Soc Nephrol 2009;20:629-37; N Engl J Med 1987;317:1098; Pediatr Clin North Am 1987;34:571-90; Pediatr Nephrol 1996;10:709-11; Pediatr Nephrol 2003;18:981-5; Pediatr Nephrol 2010;25:2321-6.

F. Off-Label Medication Use in Pediatric Patients

1. Off-label medication use: Defined as the use of a medication outside its FDA label-approved indications, which include the age group in which a medication is used, the disease or illness it treats, and the route of administration (Arch Pediatr Adolesc Med 2007;161:282-90)
 - a. About one in every four pediatric patient visits is associated with the use of off-label medication. Higher rates of off-label medication use were observed in the inpatient and ambulatory setting, which were 53.9% and 54.2%, respectively (Hosp Pediatr 2019;9:186-93).
 - b. Off-label use of medication is legal and well accepted as long as the use is based on appropriate clinical judgment. In fact, such practices are noted by the AAP as especially important and complex for patients younger than 2 years and those with chronic and/or rare diseases (Pediatrics 2014;133:563-7).
 - c. Limitations to off-label medication use include:
 - i. Potential for denied insurance provider coverage of the medication
 - ii. Possible medical liability because of serious adverse effects
 - iii. Limited experience for treatment of a condition or specific age group (e.g., neonates)
 - iv. Limited available formulations for use in young populations
 - d. A strong need remains for additional clinical trials to determine the appropriateness of selecting and dosing medications in the pediatric population.

2. Regulatory changes have been made to decrease the off-label use of medications in the pediatric population.
 - a. The Pediatric Rule, issued in 1994, permitted manufacturers to label drugs for pediatric use on the basis of extrapolated efficacy data and additional pharmacokinetic/pharmacodynamic (PK/PD) data specific to the pediatric population when disease and therapy response were considered similar to those of their adult counterparts (PREA 2003).
Limitations: This permission resulted in only a few well-conducted studies regarding infants and children because of the difficulties involved in predicting dose-response from adult data.
 - b. The Food and Drug Administration Modernization Act (FDAMA) followed in 1997, offering a financial incentive of extended market exclusivity for 6 months for performing pediatric studies. Because of the FDAMA, additional drugs were assigned pediatric labeling (FDA 2007).
Limitations: Efficacy data were still lacking.
 - c. An incentive-based Best Pharmaceuticals for Children Act was implemented in 2002, extending the FDAMA, including the provision from the 1997 FDAMA offering an additional 6 months of patent exclusivity for on-patent drugs being tested for pediatric use, thereby encouraging industry to conduct pediatric studies for branded products labeled only for adults (Best Pharmaceuticals for Children Act).
Limitations: 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.
 - d. The Pediatric Research Equity Act of 2003 also provided potential requirements for the pediatric assessment of drug applications submitted to the FDA for approval in adults (PREA 2003). This assessment included the potential use and evaluation of risk-benefit in pediatric patients.
 - e. The FDA Safety and Innovation Act legislation made the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act permanent in 2012 (FDA 2018).
 - f. The Orphan Drug Act supports the development of needed treatment of rare diseases with an occurrence of 200,000 people or fewer in the United States, such as inborn errors of metabolism (Orphan Drug Act – Relevant Excerpts).
3. A wide range of evidence in pediatric medication therapy through the identification of well-designed, appropriate biomedical literature is needed to provide optimal, evidence-based care to the pediatric population.
 - a. 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, is recommended, though individualized application to specific pediatric patients is necessary (HHS 2007).
 - b. Because of limited pediatric-specific guidelines for much of medication therapy, use of the primary literature is crucial in providing evidence-based care to infants, children, and adolescents.
 - i. 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 applicability of the results in clinical practice.
 - ii. Evaluation of literature includes appropriateness of study design, generalizability to the population under study, and appreciation for the statistical and clinical significance of findings.
 - iii. Furthermore, case reports and case series can provide some data regarding unknown effects of newer medication therapy. However, given the small patient populations in these reports, health care professionals should assess the appropriateness of applying them to their own patients.

4. Clinical judgment should be applied when considering off-label medication use and dosing in instances of limited pediatric data, and patients should be monitored to ensure desired outcomes.
 - a. Considerations when dosing medications in pediatric patients:
 - i. Body weight, BMI, or BSA, whereas adult dosing often involves a standard dose for most of the population
 - ii. Age (e.g., neonate vs. infant vs. child vs. adolescent)
 - iii. Rounding of doses, 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 and accuracy of measurement. Some institutions round doses by 10%–20%, depending on the risks associated with a given medication.
 - b. If there is no alternative therapy or when limited or no pediatric data exist for dosing but evidence supports the drug's safety in pediatric patients, some clinicians may elect to dose on the basis of the BSA ratio if the child is in the normal range for height and weight for age.
 - i. Of note, however, this is not a well-studied approach to off-label medication dosing, and caution should be used when considering this option.
 - ii. 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.
 - c. In the past, approaches to dosing included different rules, such as Fried's rule, Young's rule, and Clark's rule, to estimate dosing when pediatric-specific data were not available. However, these approaches oversimplify the known complex differences between the pediatric and adult populations, thereby over- or underestimating doses in pediatric patients. Thus, these methods are no longer recommended for estimating off-label dosing in pediatric patients.

G. Medication Safety

1. Medication errors are preventable events that result from human or system flaws.
 - a. The relative distributions of pediatric error rates based on the type of errors are estimated to be 3%–37% in prescribing, 5%–58% in dispensing, 72%–75% in administering, and 17%–21% in documentation (Qual Saf Health Care 2007;16:116-26).
 - b. The types of medication prescribing and administration errors can include, but are not limited to:
 - i. Calculation: Pediatric doses are often calculated (e.g., milligram per kilogram). Calculation inaccuracies can lead to prescribed dose errors, especially when medications are compounded into intravenous solutions/admixtures or oral suspensions.
 - ii. Units of measurement: Accuracy and consistency in the units of measurement used are important in preventing calculation and prescribing errors.
 - iii. Decimal placement: Use of trailing zeros (e.g., 5.0 mg) and missing leading zeros (e.g., .5 mg) can result in 10-fold or greater errors.
 - iv. Preparation, dilution, and dispensing
 - c. Five rights of patient medication administration. As with any patient, the five rights of patient medication administration should be reviewed every time to help ensure medication safety:
 - i. Right patient
 - ii. Right drug
 - iii. Right dose
 - iv. Right route
 - v. Right time
 - d. Technological advances to reduce errors
 - i. Computerized physician order entry can provide automated medication-dosing calculators and mandatory prescription order fields (Pediatrics 2004;113:59-63).

- ii. Use of an alert-based decision support system can potentially prevent several errors; 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.
 - iii. Barcode technology has also reduced the incorrect selection and administration of medications (N Engl J Med 2010;362:1698-707).
 - iv. Use of technologies such as smart pumps for parenteral medications in daily care can decrease error rates associated with medication administration (Pediatrics 2005;116:e21-5).
- e. Despite technological advances, however, a potential for human or system error remains during the process of preparing, dispensing, and administering medications. 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.
- 2. Key Potentially Inappropriate Drugs in Pediatrics: The KIDs List (J Pediatr Pharmacol Ther 2020; 25:175-91)
 - a. In 2020, Meyers et al. published a list of medications that are potentially inappropriate for pediatric patients that is, in short, called the KIDs List. The list is similar to the Beers Criteria, first published in 1991, for older adults (Arch Intern Med 1991;151:1825-32).
 - b. The KIDs List (Table 3) includes 67 medications and/or classes of medication and 10 excipients that are potentially inappropriate in a subgroup of or all pediatric patients. Here, the potentially inappropriate medications were defined as “medications or medication classes that should generally be avoided in persons younger than 18 years because they pose an unnecessarily high risk for children and a safer alternative is available.”
 - c. Medications that were considered but not included in the KIDs List because of insufficient evidence include:
 - i. OTC cough and cold medications
 - ii. Fluoroquinolones
 - iii. Sildenafil
 - iv. Antidepressants
 - d. The KIDs List is a reference tool to guide for quality control, thereby enhancing safe medication use in pediatric patients by helping to identify high-risk medications for adverse reactions. It is not to replace clinical judgment. In fact, any of the medications included in the KIDs List may be warranted to use in specific patients or diseases.
 - e. Of note, the KIDs List contains fewer strong recommendations (68%) than the Beers Criteria (95%), which calls for more research on adverse reactions of medications in pediatric patients (J Am Geriatr Soc 2019;67:674-94).

Table 3. Medications and/or Classes of Medication and Excipients on the KIDs List

KIDs List for Children One Year and Older				
Age	Drug	Risk	Strength	Evidence quality
Avoid				
< 3 years or 10 kg (22 lb)	Darunavir (Prezista)	Seizures, death	Strong	Very low
< 6 years	Diphenoxylate/atropine (Lomotil)	Respiratory depression, death	Strong	Moderate
	Linacotide (Linzess)	Death from dehydration	Weak	Very low
	Plecanatide (Trulance)	Death from dehydration	Weak	Very low
< 10 years or 50 kg (110 lb)	Lindane	Seizure, spasm	Moderate	Low
All children	Indinavir (Crixivan)	Nephrolithiasis	Strong	High
	Paregoric	Gasping syndrome, seizures, central nervous system depression, hypoglycemia	Strong	High
	Propofol (Diprivan; avoid more than 4 mg per kg per hour for > 48 hours)	Infusion syndrome	Strong	Moderate
Caution				
< 6 years	Valproic acid	Pancreatitis, fatal hepatotoxicity	Strong	High
< 8 years	Tetracyclines	Enamel hypoplasia, tooth discoloration	Strong	High
All children	Camphor	Seizures	Weak	Low
	Dopamine antagonists*	Dystonia, respiratory depression, death	Strong	Moderate
	Lamotrigine (Lamictal)	Serious skin rashes	Strong	High
	Meperidine (Demerol)	Respiratory depression	Strong	High
	Olanzapine (Zyprexa; concern for use > 24 weeks)	Metabolic syndrome	Strong	High
	Opium tincture	Respiratory depression	Strong	High
	Salicylates (if suspicion of viral illness)	Reye syndrome	Weak	Very low
	Tramadol	Respiratory depression	Weak	Low
KIDs = key potentially inappropriate drugs in pediatrics.				
*—Specific dopamine antagonists include chlorpromazine, fluphenazine, haloperidol, metoclopramide (Reglan), perphenazine, pimozide, prochlorperazine, promethazine, trifluoperazine, and trimethobenzamide (Tigan).				
Adapted with permission from Meyers RS, Thackray J, Matson KL, et al. Key potentially inappropriate drugs in pediatrics: the KIDs List. J Pediatr Pharmacol Ther. 2020;25(3):181-184.				

KIDs List for Infants				
Age	Drug	Risk	Strength	Evidence quality
Avoid				
Neonates	Chloramphenicol	Gray baby syndrome	Strong	High
	Gentamicin ophthalmic ointment	Severe ocular reactions	Strong	High
	Macrolides (unless for pertussis or chlamydia pneumonia)	Hypertrophic pyloric stenosis	Strong	High
	Meperidine (Demerol)	Respiratory depression	Strong	High
	Midazolam (if very low birth weight)	Intraventricular hemorrhage, death	Strong	High
	Naloxone (for neonatal resuscitation)	Seizure	Strong	High
	Nitrofurantoin	Hemolytic anemia	Weak	Very low
	Opium tincture	Respiratory depression	Strong	High
	Sodium polystyrene sulfonate (if very low birth weight)	Colonic perforation	Weak	Low
	Sulfonamides (unless treating congenital toxoplasmosis)	Kernicterus	Weak	Very low
< 6 months	Dicyclomine	Apnea	Strong	Low
Teething	Benzocaine	Methemoglobinemia	Strong	High
	Lidocaine, viscous	Seizures, arrhythmia, death	Strong	High
All Infants	Carbinoxamine	Death	Strong	Low
	Codeine	Respiratory depression, death	Strong	High
	Darunavir (Prezista)	Seizures, death	Strong	Very low
	Diphenoxylate/atropine (Lomotil)	Respiratory depression, death	Strong	Moderate
	Dopamine antagonists*	Dystonia, respiratory depression, death	Strong	Moderate
	Indinavir (Crixivan)	Hyperbilirubinemia, nephrolithiasis	Strong	Low
	Ivermectin (Stromectol; oral)	Encephalopathy	Weak	Low
	Linacotide (Linzess)	Death from dehydration	Weak	Very low
	Lindane	Seizure, spasms	Moderate	Low
	Loperamide (Imodium)	Ileus, lethargy	Strong	High
	Malathion (Ovide)	Organophosphate poisoning	Weak	Very low
	Mineral oil	Lipid pneumonitis	Strong	Low
	Paregoric	Gaspings syndrome, seizures, central nervous system depression, hypoglycemia	Strong	High
	Plecanatide (Trulance)	Death from dehydration	Weak	Very low
	Propofol (Diprivan; avoid more than 4 mg per kg per hour for > 48 hours)	Infusion syndrome	Strong	Moderate
	Sodium phosphate enema	Acute kidney injury, arrhythmia, death	Strong	High
	Topical corticosteroids (medium potency and stronger for diaper dermatitis)	Adrenal suppression	Strong	Low
	Valproic acid	Pancreatitis, fatal hepatotoxicity	Strong	High
	Verapamil	Asystole	Weak	Low
<i>continues</i>				

KIDs = key potentially inappropriate drugs in pediatrics.

*—Specific dopamine antagonists include chlorpromazine, fluphenazine, haloperidol, metoclopramide (Reglan), perphenazine, pimozide, prochlorperazine, promethazine, trifluoperazine, and trimethobenzamide (Tigan).

KIDs List for Infants				
Age	Drug	Risk	Strength	Evidence quality
Caution				
Neonates	Atazanavir (Reyataz)	Kernicterus	Weak	Very low
	Ceftriaxone	Kernicterus	Weak	Very low
	Chlorhexidine (Peridex; if very low birth weight)	Chemical burn	Strong	Low
	Dicloxacillin	Kernicterus	Weak	Very low
All Infants	Camphor	Seizures	Weak	Low
	Daptomycin (Cubicin)	Neuromuscular and skeletal adverse effects	Weak	Very low
	Difluprednate (Durezol)	Increased ocular pressure	Weak	Low
	Meperidine	Respiratory depression	Strong	High
	Opium tincture	Respiratory depression	Strong	High
	Salicylates (if suspicion of viral illness)	Reye syndrome	Weak	Very low
	Tetracyclines	Affects bone development in premature neonates, enamel hypoplasia	Strong	Moderate
	Tramadol	Respiratory depression	Weak	Low
KIDs = key potentially inappropriate drugs in pediatrics.				
*—Specific dopamine antagonists include chlorpromazine, fluphenazine, haloperidol, metoclopramide (Reglan), perphenazine, pimozide, prochlorperazine, promethazine, trifluoperazine, and trimethobenzamide (Tigan).				
Adapted with permission from Meyers RS, Thackray J, Matson KL, et al. Key potentially inappropriate drugs in pediatrics: the KIDs List. J Pediatr Pharmacol Ther. 2020;25(3):181-184.				

Source: Arnold MJ. Key Potentially Inappropriate Drugs in Pediatrics: The KIDs List. Am Fam Physician 2021;103:633-6.

H. Challenges of Medication Adherence

1. Adherence: Defined as “the extent to which a person’s behavior in taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (WHO 2003)
 - a. Medication adherence is a challenge for all patient populations, including pediatric patients. Furthermore, infants and young children must rely on a caregiver’s ability to ensure medication adherence.
 - b. Although chronic illnesses, such as cystic fibrosis and diabetes, are often associated with a high potential for poor adherence, short treatment courses, such as antibiotic regimens, are also important (N Engl J Med 2005;353:487-97).
 - c. Medication adherence is often difficult to document in ambulatory care practice environments.
 - i. Approaches to measuring medication adherence include (Pediatr Clin North Am 1997;44:1-14; Pediatr Drugs 2007;9:283-8):
 - (a) Self-report
 - (b) Health care professional’s impression
 - (c) Dose count (e.g., pills or inhaler counter)
 - (d) Refill verification
 - (e) Electronic dose monitoring services
 - (f) Monitoring of serum drug concentrations, when appropriate
 - ii. Devices such as electronic monitors have been used in research settings. However, these are not commonplace in clinic settings and are currently cost-prohibitive for routine use (Comput Inform Nurs 2011;29:489-95; Pediatrics 2005;115:e718-24).

2. Nonadherence: Defined as adhering to a prescribed therapy less than 80% of the prescribed times; is multifaceted
 - a. Is seen in all age groups, from infancy to adolescence
 - b. Reasons for poor adherence include:
 - i. Incorrect timing because of forgetting to administer or take a dose
 - ii. Conflict with caregiver's and/or patient's personal beliefs
 - iii. Socioeconomic limitations
 - iv. Adverse drug effects
 - v. Unpleasant or inconvenient medication formulation or schedules
 - vi. Psychological factors, such as peer acceptance among adolescents
 - c. In general, children younger than 5 years have greater medication adherence to the treatment of chronic illnesses, usually because of caregivers' responsibility and action in administering necessary medications (Pediatr Drugs 2007;9:283-8). However, it should not be assumed that all caregivers adhere to prescribed treatment regimens.
 - i. One reason for poor adherence in this subpopulation is apprehension regarding medication adverse effects. An example is nonadherence to inhaled corticosteroid therapy for asthma because of the fear of growth suppression.
 - ii. Other reasons for nonadherence in this younger population can include the caregiver's inability and unavailability to administer the drugs in a timely manner (Pediatr Drugs 2007;9:283-8).
 - d. Inappropriate measurements of a medication dose can also affect medication adherence.
 - i. 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.
 - ii. 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.
 - iii. Thus, caregivers should be provided with and educated about proper measuring devices such as oral syringes.
 - e. Some caregivers may also miss doses because of resistance from the child.
 - f. As a child grows older and enters early adolescence, responsibility for medication administration shifts 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 (Semin Cutan Med Surg 2010;29:137-40):
 - i. Peer pressure
 - ii. Perceived invisibility
 - iii. Potential for oppositional or rebellious behavior
 - g. Consequences of nonadherence include:
 - i. Delayed or lack of clinical improvement
 - ii. Worsening of illness
 - iii. Unnecessary therapy modifications that can lead to adverse clinical outcomes
 - iv. Increased health care use (Pediatrics 2013;132:730-40)
3. Approaches to improve medication adherence
 - a. Behavioral and educational approaches such as motivational interviewing have received the most emphasis in studies regarding chronic diseases such as pediatric asthma and diabetes (Health Psychol 1992;11:190-8; J Pediatr Psychol 2003;28:323-33).
 - b. 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.

- c. 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.
 - d. Use of a reward system and positive reinforcement may help decrease resistance by young children during treatment periods.
 - e. Empowering older children and adolescents positively with knowledge about their disease and introducing mobile health applications may improve self-management of drug therapy and medication adherence (Semin Cutan Med Surg 2010;29:137-40).
 - f. Minimizing the number of doses per day
- I. Fundamentals of Pediatric Patient Care
1. 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, PK/PD, disease, culture) and adapt approaches to suit each individual in order to provide optimal patient care. The following “checklists” are clinical pearls to keep in mind when caring for patients within each age subpopulation of pediatric patients.
 2. Infants and young children
 - a. 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.
 - b. Record body weight, height, and head circumference (for infants), and assess growth percentiles (e.g., using the WHO or CDC growth charts).
 - c. For infants, evaluate weight-based dosing regularly, especially for medications used in chronic illnesses that require dose adjustments with growth (e.g., weight gain).
 - d. Elixir formulations should be avoided because of alcohol content, especially in neonates and young infants or when chronic use or larger volumes are indicated.
 - e. Minimize use of dosage forms with preservatives (e.g., benzyl alcohol) in neonates.
 - f. Be aware of the palatability of medications – An example of a poor-tasting oral solution is clindamycin. Approaches to help alleviate unpalatable medications can include:
 - i. Using food items to help mask the unpleasant aftertaste of some medications
 - (a) Always ask about any food or medication allergies before suggesting items.
 - (b) For bitter or salty-tasting medications, chocolate may serve to mask the taste (e.g., use of chocolate syrup with doses).
 - (c) For medications with a metallic taste, fruit flavors (e.g., strawberry syrup) may help mask unpleasant taste.
 - ii. Offering a cold treat (e.g., sorbet) before and after a dose. The cold may help numb the papillae of the tongue and minimize medication aftertaste.
 - iii. Adding flavoring agents to liquid dosage formulations. Considerations when using flavoring agents are dosage form stability and compatibility with the drug to best mask its unpleasant taste.
 - g. Be aware of potential medication contraindications because of age (e.g., ceftriaxone use in premature neonates because of the potential to displace bilirubin from albumin and increase the risk of kernicterus).
 - h. Often, children around 6 years of age can swallow a tablet or capsule, but this ability should not be assumed for all children. Ask the patient and caregiver whether liquid or solid dosage forms are preferred.
 3. Older children and adolescents
 - a. Maximum doses are often adult doses; however, verify such dosing using a pediatric dosing reference. A common body weight at which adult dosing is applied is when a child’s weight reaches 40 kg (J Pediatr Pharmacol Ther 2017;22:81-3).

- b. Consider sensitive issues that are more mature or adult in nature affecting health, including alcohol, tobacco, illicit drug use, sexual activity, and psychosocial concerns.
 - c. Adolescence is often considered a “nadir” of medication adherence; thus, education and age-appropriate approaches to improve adherence should be initiated.
 - d. Be aware of the need for increasing independence, including medication administration.
 - e. Involve the patient as an active participant in overall care.
 4. Overall medication therapy assessment (PPA Position Statements; Am J Hosp Pharm 1991;48:2475-7; Am J Hosp Pharm 1994;51:1690-2; Pharmacotherapy 2005;25:1277-82): The following are examples of general items that should be considered and assessed as part of selecting, using, and monitoring medication therapy for all pediatric patients:
 - a. Use correct age, weight (in kilograms), and height.
 - b. Consider social factors such as patient or caregiver health beliefs and culture.
 - c. Correctly use units of measurement such as dose (e.g., milligram vs. gram) and body weight (e.g., kilogram vs. pound).
 - d. Calculate and verify doses by body weight (e.g., actual, ideal, adjusted) as appropriate.
 - e. Do not crush or modify extended- or sustained-release solid dosage forms.
 - f. Evaluate current conditions and determine optimal drug therapy for such conditions.
 - g. Consider comorbidities.
 - h. Evaluate appropriateness of current medication therapy, including complementary and alternative medications, supplements, and OTC drugs.
 - i. Assess medication adherence.
 - j. Be careful about inappropriate abbreviations and notations such as use of trailing zeros (e.g., 1.0 mg) and missing leading zeros (e.g., .1 mg).
 - k. Evaluate for potential adverse drug effects (i.e., ask open-ended questions of patients and caregivers).
 - l. Evaluate for drug-drug, drug-food, and drug-disease interactions.
 - m. Round doses to measurable amounts. Dose rounding (e.g., by 10% to the closest measurable dose) is common practice. Dose rounding should be avoided in medications with a narrow therapeutic index (e.g., digoxin).
 - n. Develop a monitoring plan for drug therapy with identification and assessment of the values for efficacy or safety.
 - o. Reconcile medications and dosage regimens at each patient encounter.
 - p. Provide patient and caregiver education. Not a one-time activity; education should be reinforced at several points of care (e.g., hospital, clinic, pharmacy) during care transitions
- J. Present and Future of Pediatric Pharmacy Practice
1. Pediatric patients are seen in all health care settings, including community pharmacies, ambulatory clinics, community hospitals, and large academic, tertiary medical centers.
 2. A fundamental understanding of the needs of this special population is essential for the provision of patient care by all pharmacists.
 3. 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.
 - a. This area of practice will continue to grow with its expansions in the professional pharmacy school curriculum, including specialty pediatrics tracks for doctor of pharmacy (Pharm.D.) degrees as well as continued education and training in pediatric postgraduate residency and fellowship programs.
 - b. 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 ICUs to specialty clinics such as cystic fibrosis centers nationwide.

- c. Opportunities exist to advance pediatric practice for present and future generations of pharmacists, including expanding the role of pharmacists in areas such as:
 - i. Pediatric immunizations
 - ii. Chronic care management
 - iii. Continuity of care between inpatient and outpatient care
 - iv. Pharmacotherapy research
 - v. Clinical pharmacogenomics
 - 4. Precision medicine and clinical pharmacogenomics
 - a. In its position statement, the Pediatric Pharmacy Association recognizes clinical pharmacogenomics as an emerging specialty area in which its applicability and importance to pediatric pharmacotherapy will continue to expand (J Pediatr Pharmacol Ther 2011;16:118-22). More than 300 medications now include pharmacogenomic information in their labeling (see FDA Table of Pharmacogenomic Biomarkers).
 - b. Although education and training opportunities in clinical pharmacogenomics extend through the Pharm.D. curriculum, postgraduate training, and continuing education, integration of clinical application with pediatric considerations is still limited (J Pediatr Pharmacol Ther 2018;23:499-501).
 - i. The Accreditation Council for Pharmacy Education (ACPE) “Standards 2016” include pharmacogenomics as a required content area of the didactic Pharm.D. curriculum of which graduating students are expected to be “practice-ready” to integrate genetic information for individualization of medication therapy. However, experiential learning opportunities are limited, with few programs offering electives in precision medicine and clinical pharmacogenomics.
 - ii. Postgraduate training in clinical pharmacogenomics
 - (a) For the 2022–2023 residency year, only nine PGY2 clinical pharmacogenomics pharmacy residency programs were available in the United States. Of these, only five had obtained full accreditation status from the American Society of Health-System Pharmacists (ASHP Online Residency Directory).
 - (b) Fellowship and graduate programs are available but are typically research focused.
 - iii. Professional development opportunities include:
 - (a) Self-paced education programs, such as the Pharmacogenomics Education Program (PharmGenEd)
 - (b) Certificate programs, such as the Test2Learn program
 - c. As a result, there is an increased need to incorporate clinical applications into education and training for students as well as pharmacists.
- K. Additional General Pediatric Resources
 - 1. Additional information regarding pediatric patient care, including medication dosing, extemporaneous compounding, and an overview of general pediatric diseases, can be found in various resources, including the internet and print books. Figure 1 lists examples of the general pediatric resources.
 - 2. With the growth in information technology, many drug-dosing references are also available by smartphone or tablet devices.
 - 3. Pharmacists caring for pediatric patients should have access to at least one reference on:
 - a. Pediatric-specific dosing
 - b. General pediatric disease pathophysiology and treatment options

Websites • American Academy of Pediatrics (AAP) - www.aap.org • Pediatric Pharmacy Association (PPA) - www.ppag.org
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Figure 1. Examples of general pediatric resources.

*Available in print and electronically.

II. COMMUNICATIONS WITH PEDIATRIC PATIENTS AND CAREGIVERS

A. Introduction

Communications are essential components of health care that help ensure adherence to therapy, patient safety, improved outcomes, and patient satisfaction. This section reviews the benefits associated with communicating with pediatric patients about medications as well as the techniques for delivering age-appropriate information and gaining rapport with patients and their caregivers.

1. Once the medication leaves the pharmacy, the responsibility to ensure appropriate dosing and administration shifts to the pediatric patients and their caregivers.
2. Many unintentional overdoses occur each year because of improper dose measurement and accidental drug ingestion. Difficulty measuring the proper dose can result from low health literacy or a simple misunderstanding of the directions (Arch Pediatr Adolesc Med 2008;162:814-22; Arch Pediatr Adolesc Med 2010;164:181-6).
3. Patient and caregiver education should be provided in all patient care settings. Reinforcement of essential points is critical in optimizing medication adherence, efficacy, and safety.
 - a. Transitions of care should include clear communication between the inpatient and outpatient clinic and/or community pharmacy settings.
 - b. Pharmacists can bridge the gaps in care transitions by encouraging patients and their caregivers to ask questions and proactively providing appropriate dosing devices and information about current medications during care transitions.

B. Communication Principles for Children and Adolescents

1. Children can generally begin providing and receiving information during health care visits at 3 years of age, with an even greater level of involvement starting at 7 years of age (Pediatrics 2009;124:S282-8).
2. The goals of communications with children can be to:
 - a. Obtain information from the child
 - b. Express empathy with the child

- c. Relay information to the child
 - d. Confirm the child's understanding
- C. Cognitive Developmental Stages
- When communicating with children, pharmacists should ensure the message is delivered at a level the child can understand. Identifying a child's developmental stage can help narrow the scope of information to be communicated and improve efficiency and effectiveness.
1. Piaget's classification of cognitive development: The four stages of cognitive development are as follows:
 - a. Sensory motor
 - b. Preoperational
 - c. Concrete operational
 - d. Formal operational
 2. Table 4 describes Piaget's developmental stages and how to apply them to those receiving medication education (Am J Nurs 2002;102:34-41; Res Soc Admin Pharm 2008;4:98-114).
 3. When staging a child's developmental level, it is important to recognize that the stages are estimates and that they vary among patients. Pharmacists should assess each child individually for the level of development, and then educate the child at that level.
 - a. As children are exposed to situations and experiences, they may enter a new developmental stage more quickly than children who have not had the same experiences (Pediatrics 2009;124:S282-8).
 - b. Traditional methods of staging development do not apply to children with learning disabilities or disease states that impair development (e.g., autism spectrum disorders).

Table 4. Piaget's Cognitive Developmental Stages and How They Affect Medication Education

Features	Medication Counseling
Sensory Motor (Birth – 2 yr)	
Do not see the connection between self and external objects	Learning about medications is not possible
Preoperational (2–7 yr)	
- Can consider only a single aspect of a situation - Can consider only the “here and now” - Have no concept of cause and effect - Have difficulty conceptualizing time - Do not understand the connection between an action and their health - Can use symbols or pictures to represent objects	- Hands-on activities are the most effective - Include the taste of medication in the education - Example of information to provide: “This medication will keep you from getting sick. You will take it when you wake up in the morning and before you go to sleep at night. Your mom or dad or the grown-up who is taking care of you will help you take the medication”
Concrete Operational (7–11 yr)	
- Can focus on many aspects of a situation - Can think about concrete events but have difficulty with hypothetical situations - Can distinguish between self and effects of the outside world - Can best understand concrete or observable situations - Can understand that diseases are preventable - Can see things from different points of view	- Give them time to ask questions, and explain concepts to them - Discuss the adverse effects of medications that should be reported to an adult - Example information to provide: “This medication will go into your lungs and make it easier for you to run and play. You will take it when you wake up and before you go to bed. If you do not take it two times a day, it will not work. You need to brush your teeth after using the medication. Work with your mom and dad or the grown-up who is taking care of you to make sure you take the medication right and remember to take the medication”

Table 4. Piaget's Cognitive Developmental Stages and How They Affect Medication Education (*Cont'd*)

Features	Medication Counseling
Formal Operational (≥ 12 yr)	
• Capable of hypothetical thought and logical reasoning • Can understand how illness occurs and how it is affected by their actions • Begin to understand they can have control of their health	• Typically, able to receive a message at the same level as an adult • Keep in mind they may be more embarrassed by certain topics • Example information to provide: • "This medication works in your lungs to decrease mucus and swelling so that you can breathe better and have less cough. Because you are breathing things into your lungs every day that cause the problem, this medication works only if used every day, twice a day. It is important to keep using this medication even when you start feeling better because the asthma will still be there. Work with your parents or adults who care for you to help make this part of your everyday routine"

Information from: ACCP 2020;3-17; Am J Nurs 2002;102:34-41; Res Soc Admin Pharm 2008;4:98-114.

D. Developing Rapport

Many children and adolescents are hesitant to talk to adults they do not know. Therefore, the pharmacist's first step is to gain the child's trust and express an interest in the child as an individual.

1. General Tips Recommended for Communicating with Children and Adolescents (Am J Nurs 2002;102:34-41; Child Care Health Dev 2006;32:321-31; Clin Ther 1999;21:1280-4; Pediatrics 2008;121:e1441-60)
 - a. Sit at or below their eye level.
 - b. Begin by discussing a topic that is of interest to the child or adolescent.
 - c. Avoid commenting on characteristics about which the child or adolescent may be self-conscious (e.g., hair color, height, body weight).
 - d. Use a normal tone of voice.
 - e. Do not "talk down" to them.
 - f. Maintain a calm and nonjudgmental demeanor.
 - g. Give them your full attention.
 - h. Listen actively and repeat information to ensure you understand them.
 - i. Be aware of their body language and then respond, if needed.
 - j. Allow them to express concerns and ask questions.
 - k. Give them ample time to respond to questions.
 - l. Consider differences in culture that may affect a person's likelihood of maintaining eye contact and interest in self-care.
2. Specific Techniques for Communication by Age Groups
 - a. Infants: The importance of gaining patient rapport starts in infancy. Although medication education cannot be delivered to infants, interacting with an infant's parents or caregivers will be much easier if the infant is at ease.
 - i. Do not lean over an infant's face. Take the infant out of the caregiver's arms only if the infant is anxious or willing to leave the caregiver. Do not force play
 - ii. Give parents or caregivers ample time to comfort their infant when the infant is irritable.
 - b. Toddlers and preschoolers: At 1–5 years of age, children are developing new skills and do not yet understand the importance of health care visits and listening to others. They often have difficulty communicating because they are learning new words and how to formulate sentences.
 - i. Show patience to give the child time to think about what to say and communicate a sentence.
 - ii. Provide a playful distraction, such as an opportunity to play with a toy, which will help redirect the child to a new activity when the child becomes distracted or disruptive.

- iii. Deliver information in simple terms, with brevity and honesty. Avoid asking the child for a prolonged recall of information because children do not have a good concept of time.
 - c. School-aged children: For school-aged children, it is easier to obtain information using open-ended questions and allowing them to explain how they perceive a situation. They will begin to provide a more accurate recall of symptoms and activities and will often give a more accurate account of their current symptoms than their parents or caregivers. Because they have a better understanding of cause and effect by this age, they will have a greater need to know information and to have a chance to express their concerns and ask questions.
 - i. Begin engaging in the decision-making process about their treatment plan. Offer alternatives for the child to choose from if they do not like a medication, and educate the child on how the alternatives differ.
 - ii. Integrate visual displays of disease states and medications because children at this age enjoy interacting with adults by way of games and challenges.
 - d. Adolescents: Adolescents may be the least likely to trust that adults have their best interest in mind and may be unwilling to provide a great deal of information.
 - i. Begin the conversation by asking about a topic that may be of interest to the adolescent.
 - ii. Recognize the adolescent as the primary person giving information during an encounter, and ask parents or caregivers to confirm or add information. Adolescents should learn to advocate for their own health care and communicate their needs.
 - iii. Remain calm and nonjudgmental even when adolescents provide information that alarms or shocks you.
 - iv. Include adolescents in the decision-making process when developing a treatment plan.
 - v. Affirm that adolescents' questions and concerns have been addressed.
 - vi. Give adolescents an opportunity to talk privately rather than in a parent's presence, especially when planning to ask the adolescent about contraception, sexual health, or alcohol, drug, or tobacco use. This approach will allow adolescents to speak more freely and will convey that you respect their privacy and perspective.
 - (a) Common situations that require privacy and sensitivity when communicating with adolescents include counseling on:
 - (1) Proper use of contraception
 - (2) Drug interactions that may increase the risk of unintended pregnancy while using oral contraception
 - (3) Interactions between alcohol and medications
 - (b) Adolescents may be unwilling to talk about these issues in a first encounter but will likely become more open after the pharmacist has developed trust in follow-up encounters.
 - (c) Parents and caregivers may resist this approach, but you should emphasize that adolescents need to learn to communicate directly with health care professionals and begin to take responsibility for their medical care.
- E. Additional Communication Considerations for Children and Adolescents

The technique and skill required for obtaining information differs from that required to deliver information.

 - 1. Use open-ended questions when obtaining information. The questions must be specific and often need to be followed up with more straightforward, closed-ended questions.
 - a. With closed-ended questions, children and adolescents may give responses that they think will please the health care professional (Child Care Health Dev 2006;32:321-31). Let pediatric patients know that it is acceptable to be honest. An example of a statement to help encourage truth in recalling medication adherence is: "A lot of people have trouble remembering to take their medicine; do you find it hard to remember to take your medicine?"
 - b. Following up with additional open-ended questions can help obtain further details.

2. Emphasize the importance of knowing the medication name and recalling it at future visits.
 - a. Children often refer to a medication by its appearance or color and sometimes what they use it for, rather than by its name.
 - b. When interviewing the patient, if the child does not know the name of the medication, ask if the child can describe what it looks like.
 3. Essential components of medication education for children include the following:
 - a. Why do I need this medicine?
 - b. How does the medicine taste?
 - c. When do I take the medicine?
 - d. How will it make me feel better?
 - e. How long will I take it?
 - f. What are the adverse effects?
 4. Educate children to tell an adult:
 - a. If they take too much medication;
 - b. If they see someone else taking their medication; or
 - c. If they have any new feelings or adverse effects while taking the medication.
 5. When a child or adolescent is asked to demonstrate a skill such as inhaler technique, smaller children may be fearful, embarrassed, or shy.
 - a. For those who are fearful or anxious, consider giving them the spacer to play with before trying to demonstrate the technique so that they learn it is not a harmful object.
 - b. For those who seem embarrassed, it is important to ensure as much privacy as possible and to consider demonstrating the technique before asking them to do so.
 - c. Consider giving children and adolescents choices, but only when a choice truly exists. For example,
 - i. It is not effective to ask “Would you like to show me how you use your inhaler?” if the intention is to have patients demonstrate the technique, even if their answer is “no.” The pharmacist will lose rapport by proceeding with having them demonstrate the technique after they have responded that they are not interested.
 - ii. A more appropriate statement might be, “I need to watch you use your inhaler so I can make sure it is working; would you like to show me now or after we talk about your medicines?”
 6. Promote medication adherence strategies that are tailored specifically to the patient. Ask children and adolescents what will help them remember to take their medications. No single approach works for everyone. Potential methods to help them remember include:
 - a. Posting dosing calendars with or without medication pictures on them
 - b. Providing mobile-based reminders or alarms
 - c. Placing the medications in an area of high visibility
 - d. Using pillboxes
 - e. Using mobile-based applications, such as Medisafe (<https://www.medisafeapp.com/>)
- F. Communicating with Parents and Caregivers
- Because children often depend on an adult caregiver to help administer and use medications, pharmacists should provide caregivers with education that is specific to the child to increase the caregiver’s confidence in the treatment.
1. Studies show that parental and caregiver satisfaction with medical care is determined by the health care professional’s interpersonal skills. If they feel that they were not treated with respect or that their fears were not addressed, they will be dissatisfied and less likely to follow through with medical advice (Pediatrics 2008;121:e1441-60).

2. General Tips Recommended for Communicating with Parents and Caregivers (Am J Nurs 2002;102:34-41; Child Care Health Dev 2006;32:321-31; Clin Ther 1999;21:1280-4; Pediatrics 2008;121:e1441-60)
 - a. Inform them you will be talking with their child or adolescent. There is a fine line between including the child in the encounter and ensuring the parents feel included as well. It is helpful for providers to let parents know that they plan to ask the child questions and to provide them with information before starting the medication.
 - b. Learn their names and use them during communication. The pharmacist is encouraged to ask parents how they prefer to be addressed. In interviews of parents during physician visits, 88% wanted to be addressed by their names rather than as “mom” or “dad” (Clin Pediatr 2009;48:720-2).
 - c. Provide guidance on how much their child should be involved in self-administering the medication.
 - d. Encourage them to provide their child with some autonomy, when appropriate.
 - e. Allow them to express concerns and ask questions.
 - f. Respond respectfully about any misconceptions or fears they express.
 - i. Written information dispensed with prescriptions is often not phrased with a child in mind and can be frightening and confusing to parents or caregivers. Many caregivers fear giving their children any medications; thus, reading this information may cause them not to give the medication.
 - ii. An example is the use of fluoroquinolones in children.
 - (a) The AAP recommends fluoroquinolones in children if no other alternatives exist for treatment of infection.
 - (b) Many patient information handouts, however, state that these medications should not be used in children because of the lack of an FDA label-approved indication and safety concerns.
 - (c) Parents or caregivers who see this information may be resistant to giving the medication to their child unless they are educated on the data that exist and informed that no alternatives exist.
 - g. Written information should be at the sixth-grade reading level to ensure understanding by those with low health literacy.
 - i. Most materials are estimated to be written at a 10th- or 11th-grade reading level (Acad Pediatr 2010;10:224-7).
 - ii. Methods of assessing readability include the Flesch-Kincaid formula (The FLESCH Grade Level Readability Formula (readabilityformulas.com)) and the McLaughlin Simple Measure of Gobbledygook (The SMOG Readability Formula, a Simple Measure of Gobbledygook (readabilityformulas.com)).
 - iii. The United States Pharmacopoeia has developed a guide to help develop and evaluate educational materials (American School Health Association 1998). This guide includes not only readability, but also the balance of words and pictures and the appropriateness of content for the child’s age. Parent-friendly medication information handouts are available that are more specific to children and easier to read (ACCP 2009). These handouts are available in English and Spanish.
 - iv. Lexicomp online also provides pediatric-specific patient education handouts in 18 languages.
3. Information Needed to Supplement Medication Information Handouts
 - a. If parent-friendly, pediatric-specific medication information handouts are unavailable, the pharmacist can point out differences that may be more relevant to the child than the information provided on the medication handout from the pharmacy.
 - b. These include:
 - i. How to measure the dose
 - ii. How to administer the medication

- iii. How the adverse effects may manifest in a child
- iv. How the warning labels apply to a child: For example, the statement “Do not operate heavy machinery while taking this medicine” has a different meaning for a child. In this case, the pharmacist should counsel parents that their child should avoid tall playground equipment and should be careful riding a bicycle or any motorized toys while taking this medication.
- v. Reassurance that the medication may be used for an indication other than those listed
- 4. Additional Communication Considerations During the Encounter
 - a. Determine who will be giving children their medication.
 - i. Medication is often given at school or by a grandparent.
 - ii. Or it may be given at another house if the parents do not live together.
 - (a) If the person accompanying the child to the visit is not the only one to administer the medication, the adult who is present at the visit should be educated on the importance of providing all information to everyone who will be responsible for administering the child’s medication.
 - (b) Providing adequate information to the school ensures the safe and appropriate administration of the medication in that setting.
 - b. Verify the person’s identity with the child. Another relative, a babysitter, or a stepparent may be with the child.
 - i. In some cases, the pharmacist may need to contact the parents if they are not at the visit to ensure they have the information needed to safely use their child’s medication.
 - ii. This practice will also help prevent uncomfortable moments that occur when the adult’s identity is assumed.

G. Present and Future of Communication with eHealth

- 1. Health care is continuously evolving and so is the method of communication between patients and health care professionals. Innovations in electronic health (eHealth) providing functions of diagnosis, treatment, self-management, monitoring, and/or communication are increasing (J Med Internet Res 2021;23:e27180).
 - a. Examples of interventions and their potential applications in eHealth (Clin Transl Allergy 2021;11:e12061):
 - i. Telemedicine: Health services are delivered through electronic and telecommunication technologies, extending beyond the limitations of physical visits between patients and health care professionals.
 - ii. Mobile health (mHealth): Mobile devices such as smartphones are integrated into the delivery of health care. Electronic diaries available on mHealth, for example, can allow monitoring of symptoms in more detail.
 - iii. Wearables: Hands-free devices, such as smartwatches, can be worn as an accessory, as clothing, or as part of the body, providing real-time information for early detection of symptom triggers.
 - iv. Natural language processing: These programs can understand human language as it is spoken, minimizing the language barriers between patients and health care professionals.
 - b. Patient empowerment: Allows patients to be more proactive in managing their own health, affecting change in the interpersonal processes between patients and health care professionals
 - c. Adjustments in structure and processes of health care: Organizational and clinical processes need to ensure that eHealth supports desired outcomes.
 - d. There is continued need for research investigating effective integration of eHealth into health care organizations and across systems.

III. EDUCATION FOR PHARMACY STUDENTS, POSTGRADUATE TRAINEES, AND PHARMACISTS

A. Introduction

In the past few decades, the evolving roles of pharmacists to provide pharmacy and patient care services have placed an emphasis on how best to educate and train pharmacy students, postgraduate trainees, and other health care professionals. This section focuses primarily on the pharmacist's role in pharmacy education and training. Nonetheless, many of the strategies described may also apply to educating other health care professionals.

1. Pharmacy education has continued to evolve into the current model, which is a hybrid of education and training paradigms.
2. The expansion of education and training programs has led to a demand for pharmacy faculty, with the greatest growth in positions available for clinician-educators.
 - a. As a result, many new pharmacists graduating from pharmacy residencies have found themselves in these clinical faculty positions shared with practice sites, with immediate responsibilities for teaching and precepting pharmacy students and residents.
 - b. At the same time, the greater emphasis on education has led to increased focus on educational research, which suggests that traditional teaching and learning methods (primarily learning through passive lectures and periodic examinations) will not suffice to prepare students for current pharmacy practice.
 - c. Figure 2 summarizes the factors that influence the need for pharmacists to become well-prepared educators and preceptors.

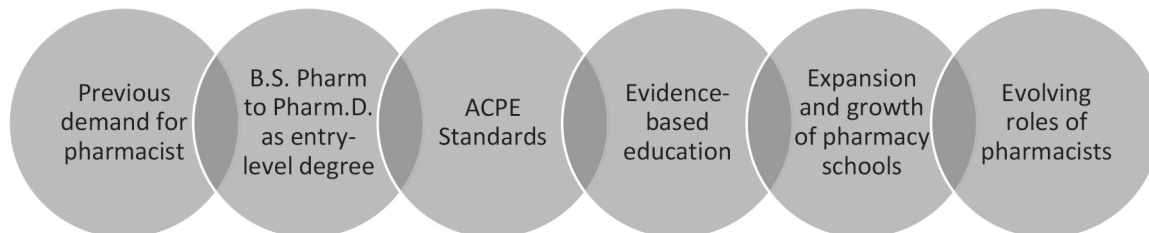


Figure 2. Factors influencing the need for pharmacists to become effective educators and preceptors.

Modified from: Hammer D. Principles and methods of educating health care professionals. In: Bernhardt MB, Blackmer AB, Cox CL, et al., eds. *Updates in Therapeutics®: Pediatric Pharmacy Preparatory Review and Recertification Course*, 2021 ed. American College of Clinical Pharmacy, 2021:1029-56.

3. In addition, the need for pediatric pharmacy training specialty practitioners persists. In 2022, although there are more than 200 pediatric medical residency programs in the United States, there are just 74 PGY2 pediatric pharmacy residency programs, of which 65 have obtained full accreditation status from the American Society of Health-System Pharmacists (ASHP Online Residency Directory; AAMC 2022). The demand for pediatric pharmacists as educators and preceptors is likely to continue with the expansion of health systems, adding pediatric towers or hospitals across the United States.

B. ACPE Standards for Pharmacy Education and Training

ACPE is the primary regulatory body for pharmacy education, both for Pharm.D. and continuing pharmacy education programs. This section describes the importance of ACPE and some of the pertinent requirements for faculty, preceptors, and Pharm.D. curricula of which all educators and preceptors should be aware.

1. The ACPE standards have evolved to advance education (and hopefully practice, through graduates) above and beyond ensuring minimal competence to practice as an outcome of training and education from accredited schools.

2. ACPE Requirements for Faculty and Preceptors: Although ACPE does not require all faculty and preceptors affiliated with pharmacy schools to have received formal training in education, it has two standards that directly address the qualitative factors of faculty, staff, and preceptors.
 - a. *Standard 19: Faculty and Staff – Qualitative Factors.* “Faculty and staff must have academic and professional credentials and expertise commensurate with their responsibilities to the professional program and their academic rank.”
 - b. *Standard 20: Preceptors.* “Preceptors must have professional credentials and expertise commensurate with their responsibilities to the professional program.”
 3. ACPE Requirements for Didactic and Experiential Curricula: Although ACPE does not dictate exactly what and how curricula are taught, it has standards that are meant to guide schools in designing and implementing didactic and experiential curricula. Certain parts of these standards directly affect individual faculty and preceptors.
 - a. *Standard 10: Curricular Design, Delivery and Oversight.* “Curricular expectations must emphasize active learning pedagogy, content integration, knowledge acquisition, application of knowledge to therapeutic decision-making, and the maturation of professional attitudes and behaviors.”
 - b. *Standard 12: Pre-APPE Curriculum.* “The Pre-APPE curriculum must provide a rigorous foundation in the biomedical, pharmaceutical, social/administrative/behavioral and clinical sciences and incorporate Introductory Pharmacy Practice Experience (IPPE) in order to prepare students for Advanced Pharmacy Practice Experience (APPE).”
 - c. *Standard 13: APPE Curriculum.* “APPE must integrate, apply, reinforce, and advance the knowledge, skills, attitudes, abilities, and behaviors developed in the Pre-APPE curriculum and in co-curricular activities.”
 4. ACPE Requirements for Interprofessional Education: Another ACPE standard that may affect many faculty and preceptors is Standard 11, which pertains to interprofessional education and training.
 - a. *Standard 11: Interprofessional Education.* “The curriculum must prepare all students to provide entry level patient-centered care in a variety of practice settings as a contributing member of an interprofessional team.
 - b. In the aggregate, team exposure must include prescribers, as well as other health professionals.”
 5. ACPE Requirements for Continuing Professional Development (CPD): ACPE’s commitment to CPD is well established in Standard 6, which pertains to a college or school’s vision, mission, and goals.
 - a. *Standard 6: College or School Vision, Mission, and Goals.* “The college or school publishes statements of its vision, mission, and goals.”
 - b. Standard 6.3 Education, scholarship, service, and practice – “The statements address the college or school’s commitment to professional education, research and scholarship, professional and community service, pharmacy practice and continuing professional development.”
 6. In summary, pharmacy educators and preceptors should understand these ACPE standards and work with their affiliated schools or colleges to achieve them. Greater detail about the ACPE standards can be found in the ACPE “Standards 2016.”
- C. Evidence Supporting Teaching, Precepting, and Learning
- Educators and preceptors need to be familiar with evidence that supports the didactic and precepting strategies used in pharmacy education and training. As with the practice of evidence-based medicine, evidence-based education suggests that the content of what is taught or practiced and the process of teaching and learning need to use evidence to promote the best learning outcomes.
1. Key findings from research
 2. These findings can guide teaching and precepting:
 - a. Good teaching and precepting can promote higher learning outcomes.

- b. Consider the learners:
 - i. Using a one-size-fits-all approach to teaching and learning does not work as well as using several strategies.
 - ii. Millennials and younger generations may not learn well with traditional learning approaches. Therefore, their learning potential may be achieved more effectively with more current strategies. In fact, AACP “supports the use and development of emerging and innovative technologies, including but not limited to games and simulation, to enhance pharmacy and interprofessional education” (Am J Pharm Educ 2014;78:S23).
 - c. Create purposeful instruction.
 - i. Instructional alignment can promote higher learning outcomes.
 - ii. Providing context and establishing relationships to practice and other content areas promote effective learning (e.g., vertical and horizontal integration).
 - iii. Active learning promotes greater learning outcomes (e.g., retention, application) than passive learning (e.g., sitting in a lecture, possibly even with note taking).
 - iv. Using readings with targeted questions or guides promotes better learning outcomes than using assigned readings alone.
 - v. Critical thinking is best developed through modeling and demonstration.
 - vi. Writing improves critical thinking, learning retention, and application.
 - vii. Long lectures (even as short as 50 minutes) do not hold students’ attention as well as short, punctuated lectures.
 - viii. Thoughtful repetition and scaffolding (i.e., going from simple to complex in a logical sequence) can promote better learning outcomes.
 - d. Provide assessments and feedback.
 - i. Frequent assessment with feedback leads to higher learning outcomes.
 - ii. Specific, objective, immediate feedback can improve learning outcomes.
- D. Current Educational Frameworks and Guiding Philosophies
- 1. Learner-Centered Education
 - a. An educational framework that focuses on:
 - i. What the learner is learning
 - ii. How the learner is learning
 - iii. The conditions under which the learner is learning
 - iv. Whether the learner is retaining or applying the learning
 - v. How current learning prepares the learner for future learning
 - b. In the learner-centered model, educators and preceptors need to consider themselves as coaches and facilitators rather than storers of knowledge and wisdom to which learners have access.
 - 2. Ability-Based Education (ABE)
 - a. An educational framework that focuses on:
 - i. Development of learners’ abilities (rather than knowledge only)
 - ii. Use of assessment as part of the learning process and not just as a finale
 - b. Definitions
 - i. Ability: Includes components of knowledge, skill, and attitude
 - ii. Learning outcome: Statement that describes what a learner should be able to do at the end of a program
 - iii. Ability-based outcome (ABO or ability outcome): Learning outcome that combines knowledge, skills, and (possibly) attitudes

- c. Mapping of ABOs: Many schools use ABOs at one or more levels. Ideally, each set of ABOs is mapped back to the set that precedes it, as shown in Figure 3. This helps ensure that all ABOs are being covered in the curricula and that unnecessary material is reduced.

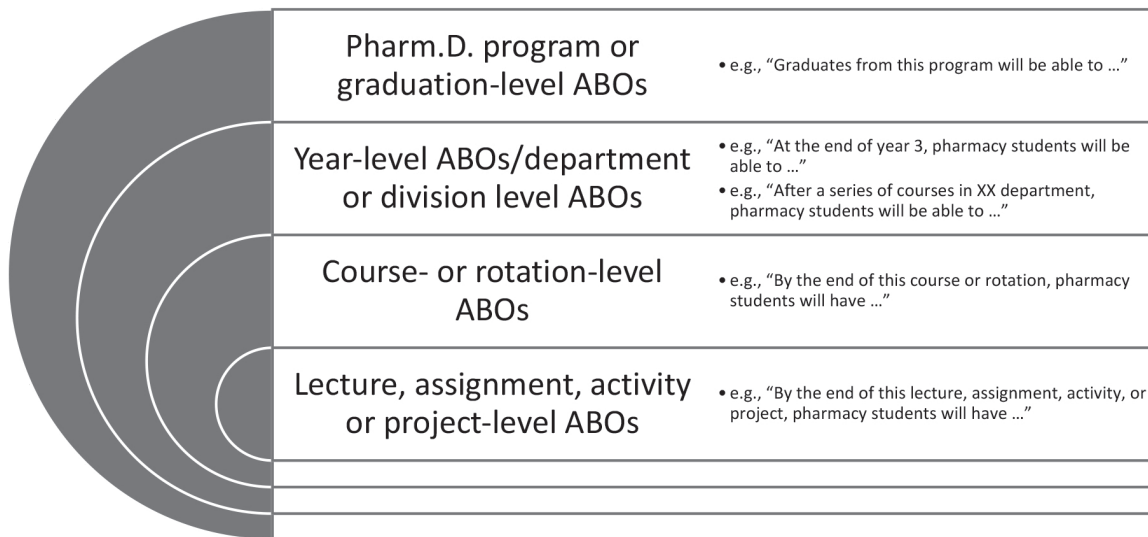


Figure 3. Relationship of ABOs from a learning activity level to a program or graduation level.

ABO = ability-based outcome.

Modified from: Hammer D. Principles and methods of educating health care professionals. In: Bernhardt MB, Blackmer AB, Cox CL, et al., eds. Updates in Therapeutics®: Pediatric Pharmacy Preparatory Review and Recertification Course, 2021 ed. American College of Clinical Pharmacy, 2021:1029-56.

- i. Typically, the ABOs of each lecture, assignment, activity, or project for any given course or rotation map back to the ABOs of the course or rotation. This allows the course director or primary preceptor to ensure that all course or rotation ABOs have been met by these lectures, assignments, activities, or projects.
 - ii. Similarly, the ABOs of a course or rotation for any given academic year (or program, such as IPPE or APPE) should map back to the ABOs of the academic year, department, or division, confirming that all academic year, department, or division ABOs have been met.
 - iii. Finally, the ABOs of an academic year, department, or division (or ABOs of course or rotation if ABOs of academic year are unavailable) should map back to the ABOs of program or graduation level.
- d. Applying ABE: Figure 4 describes the steps to applying ABE.



Figure 4. Steps of providing ability-based education.

ABO = ability-based outcome.

Modified from: Hammer D. Principles and methods of educating health care professionals. In: Bernhardt MB, Blackmer AB, Cox CL, et al., eds. Updates in Therapeutics®: Pediatric Pharmacy Preparatory Review and Recertification Course, 2021 ed. American College of Clinical Pharmacy, 2021:1029-56.

- i. Each ABO should be broken down into its knowledge, skill, or attitude. Each ABO should contain only one idea (e.g., knowledge, skill, or attitude).
 - ii. Instructions and assessments (e.g., lectures, assignments, projects, activities, reviewing old examinations) should allow learners to “practice” the ABOs.
 - iii. Explicit assessment criteria are used to evaluate achievement of the ABOs and allow learners to know how they will be assessed.
 - iv. Feedback should be based on the developed criteria so that the learners know how and where to improve their performance. Feedback should be:
 - (a) Specific
 - (b) Objective
 - (c) Constructive
 - (d) Timely
3. Instructional Alignment: Defined as ensuring the learning objectives, instructional strategies, and assessment are aligned
4. Continuing Professional Development (CPD)
 - a. Defined by ACPE as “a self-directed, ongoing, systematic and outcomes-focused approach to life-long learning that is applied into practice” (ACPE Continuing Professional Development). The concept was first introduced in the pharmacy profession by the International Pharmaceutical Federation.
 - b. Elements of the CPD model described by ACPE include (Am J Pharm Educ 2018;82:6461):
 - i. Reflect: Assess the needs and goals for personal and organizational growth.
 - ii. Plan: Develop plans for learning activities that align with the intended outcomes.
 - iii. Learn: Implement the learning plan into effect.
 - iv. Evaluate: Assess achievement of the intended outcomes.
 - v. Apply: Incorporate the learned outcomes into practice.
 - vi. Record and review: Document and review the learning process during all stages to allow identification and achievement of CPD.
 - vii. Figure 5 shows an example of implementing CPD in practice.
 - c. Figure 6 shows examples of CPD activities (ACPE Guidance on CPD).
 - d. Other CPD models exist such as the International Pharmaceutical Federation model and the ADVANCE model by the American Pharmacists Association, which may vary slightly. The processes for pharmacists to engage in CPD, however, are similar (Pharmacy (Basel) 2020;8:157).

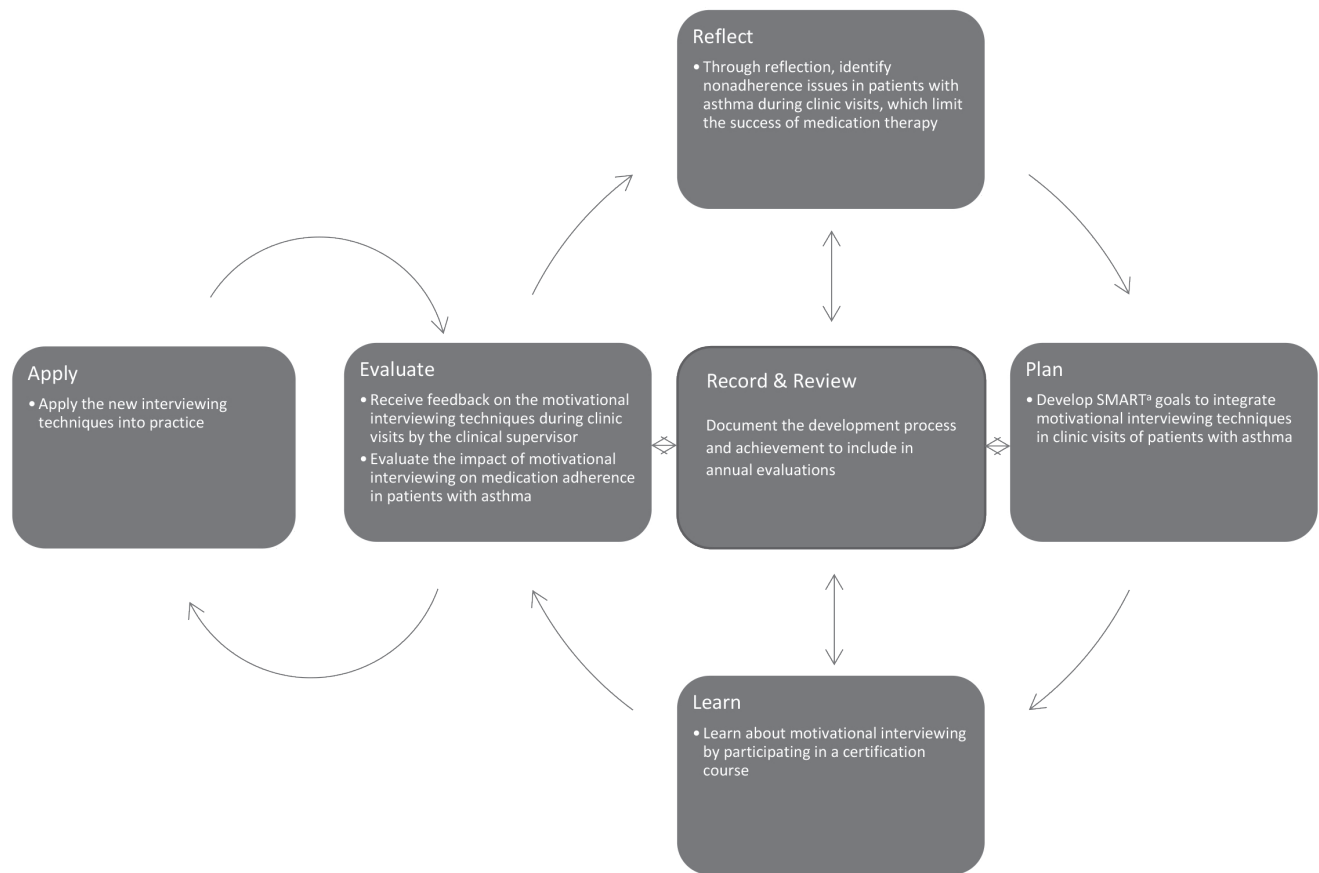


Figure 5. Example of implementing continuing professional developing in practice.

SMART = specific, measurable, achievable, relevant, and time-bound.

Adapted from: Wheeler JS, Chisholm-Burns M. The benefit of continuing professional development for continuing pharmacy education. Am J Pharm Educ 2018;82:6461.



Figure 6. Examples of continuing professional development by types of activities.

CPE = continuing pharmacy education.

Adapted from: Accreditation Council for Pharmacy Education (ACPE). Guidance on Continuing Professional Development (CPD) for the Profession of Pharmacy. Available at <https://www.acpe-accredit.org/pdf/CPDGuidance%20ProfessionPharmacyJan2015.pdf>.

5. Bloom and Krathwohl's and Fink's taxonomies and Miller's pyramid: These taxonomies have been used widely in education to design, assess, and diagnose student learning. They provide structure and focus to teaching and learning.
 - a. Bloom et al. originally defined levels of learning for three learning domains: a cognitive domain for mental skills and knowledge, a psychomotor domain for manual or physical skills, and an affective domain for attitudes and emotional growth.
 - i. The cognitive domain is the most widely used in education.
 - ii. These taxonomies can be extremely helpful when creating objectives, instructions, and assessments designed to tap into specific levels of learning, as shown in Figure 7.

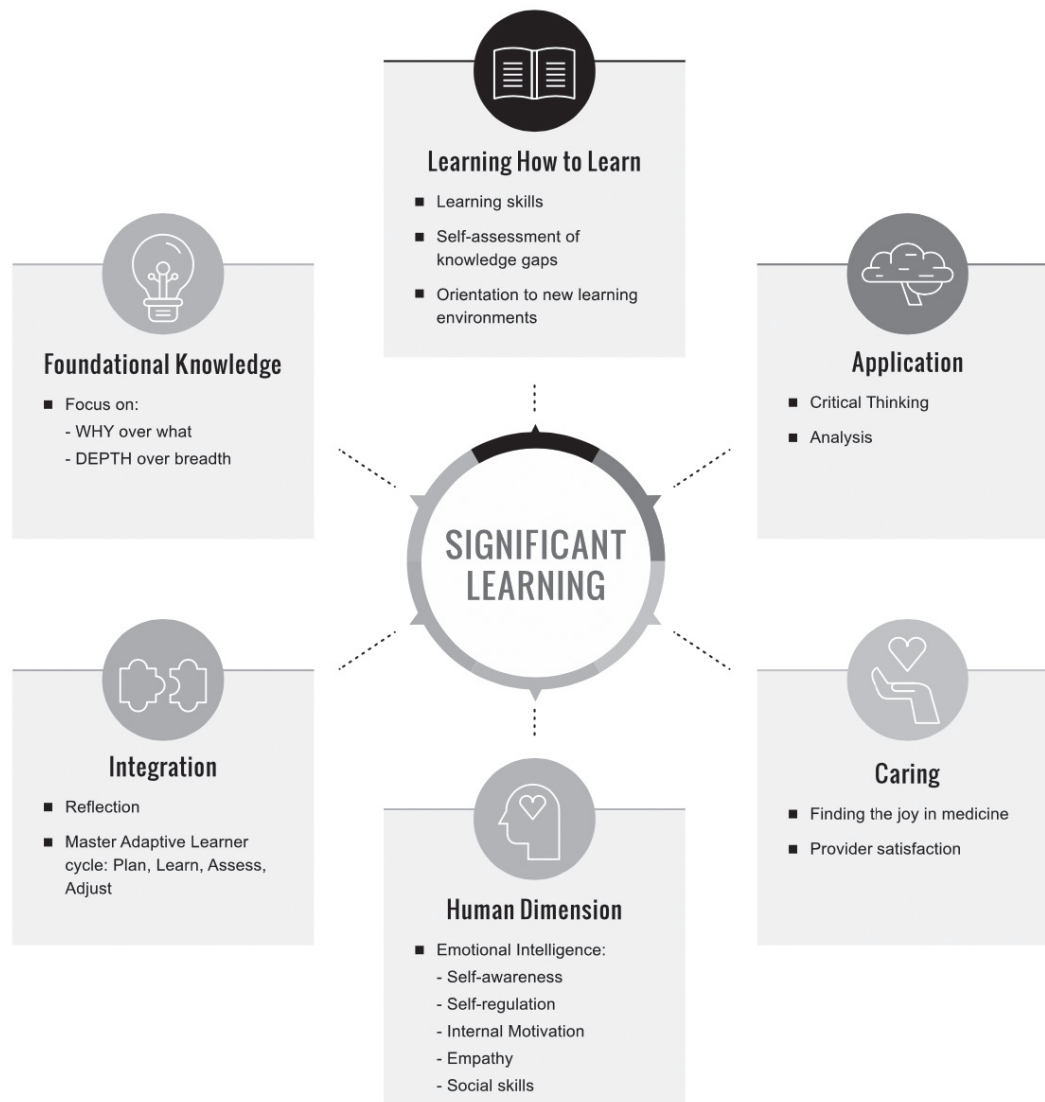


Figure 8. Fink's taxonomy of significant learning.

Information from: Branzetti J, Gisondi MA, Hopson LR, et al. Aiming beyond competent: the application of the taxonomy of significant learning to medical education. Teach Learn Med 2019;31:466-78.

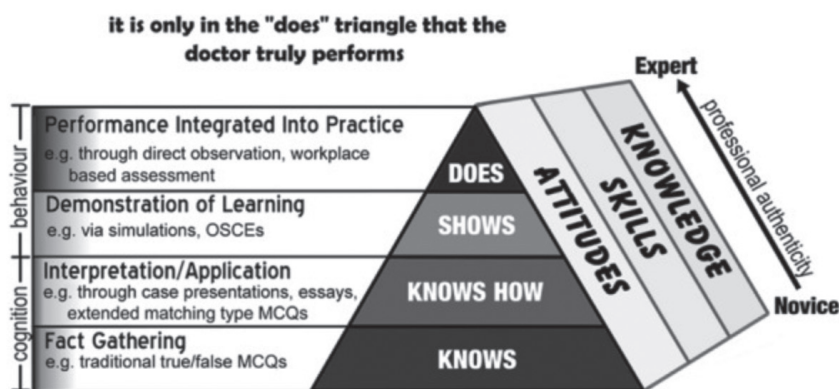


Figure 9. Miller's pyramid.

MCQ = multiple choice question; OSCE = objective structured clinical examination.

Information from: Emerg Med Australas 2015;27:173-5; Acad Med 1990;65:63-7. Adapted by Drs. R. Mehay and R. Burns, UK (Jan 2009).

E. Designing Instruction to Achieve Learning Outcomes

Whether teaching in the classroom or precepting at the practice site, educators and preceptors should plan purposeful learning experiences for their learners.

1. Questions to Ask Yourself

- What will help learners practice and achieve the learning outcomes and objectives? (see the ABE framework)
- What is realistic for learners to accomplish? (e.g., consider workload, credit load)
- How much time will be necessary to assess and provide constructive feedback for learners? (e.g., consider how many subjective, objective, assessment, plan [SOAP] notes you can grade)

2. Technology in the Classroom

- Before integrating any technologies into the classroom, evaluate whether using the technology will help learners achieve the learning outcomes and objectives.
- Orient the technology to learners to increase their experience and minimize technical barriers.
- Create a backup plan.
- Table 5 lists examples of the current technologies available for the classrooms. (Note: This is not an inclusive list.)

Table 5. Examples of Technology Used in Classrooms (not inclusive)

Learning management systems	- e.g., Blackboard, Canvas - Allow integration of: - Interactive presentations (e.g., VoiceThread) - Discussion boards - Collaborative mind mapping (e.g., Mindomo) - Audio/video feedback - Verification for plagiarism (e.g., Turnitin)
Computerized testing	- e.g., ExamSoft - Allow to lock down browsers
Audience response systems	- e.g., Poll Everywhere, iClickers, Kahoot, Quizizz, Quizlet - Increase engagement and enable evaluation of understanding
Simulation	- High-fidelity simulations (e.g., robotics, SimMan) - Virtual patients (e.g., electronic medical records)
Mobile applications	- Podcasts - Social media (e.g., Twitter)

3. Instructional Techniques for the Classroom: Active learning techniques should be used purposefully to help learners achieve the learning objectives or ABOs and not simply to keep them engaged or entertained.

- Problem-based learning (PBL):** Learners work in groups in a self-directed way. Given a particular scenario or problem, learners discuss what they already know, identify what they need to know, and decide how and where to access information that will help them solve the problem. Instead of “teaching,” instructors act as “tutors” by supporting, guiding, and monitoring the learning process.
- Team-based learning:** This strategy is similar to PBL but is more structured. Learners are placed in teams for a time interval (e.g., a semester) and are individually responsible for completing pre-readings and assignments before meeting with the team in class. An individual readiness assurance test is administered individually to ensure the outside readings were completed, followed by the team readiness assurance test that is taken again with the team.
- Case-based learning:** This strategy is similar to PBL but uses real-life cases to focus on learners’ application of knowledge to work through cases.

- d. Flipped classroom: Learners view a lecture or complete readings before coming to class. The time in class is used to engage in case or other discussions, facilitated by the instructor.
- e. Enhanced lecture: Mini-lectures (10–20 minutes) are punctuated with active learning strategies (described in the text that follows) or breaks.
 - i. Think-pair-share: This is a 2- to 5-minute exercise.
 - (a) A question is posed to learners.
 - (b) Individually, learners think about it and write down their responses for a brief time (e.g., 1 minute).
 - (c) In pairs, learners then discuss their responses with the person next to them.
 - (d) Subsequently, learners share their responses with the instructor and the rest of the class.
 - ii. One-minute paper: After a lecture, mini-lecture, or activity, learners are asked to respond to a few questions, such as:
 - (a) “What is something you learned today that you can use immediately?”
 - (b) “What is something you are still confused by?”
 - (c) “What constructive feedback do you have for the instructor today?”
 - iii. Muddiest point: This strategy is similar to a one-minute paper except that it specifically focuses on the learner’s question about something that confuses them. Learners then take a break or are dismissed while the instructor reviews the questions and responds to those that were most common. The response may be provided live when meeting again with learners, by email, or in another form of communication.
 - iv. Pausing: Taking short breaks, even for just a minute or so to let learners stretch, ask a question, or compare notes, has been shown to improve learning.
 - v. Sharing notes: Deliberately have learners take a few minutes to share their notes with the person next to them to see differences and discuss them. This is a good collaborative learning technique.
 - vi. Writing examination questions: Learners will create questions that correspond to the learning objectives for an upcoming quiz or examination. The activity can be used during class, at the end of a section or lecture, or as an assignment after class.
4. Instructional Techniques for Experiential Learning: Experiential learning does not necessarily imply active learning. Some experiential activities are more passive, such as shadowing or observing. Although some passive learning may be necessary, experiential learning should be made as active as possible for learners to promote the greatest learning outcomes, especially the development of comfortable independence and confidence. Thoughtful, well-planned experiential learning activities can benefit the preceptor as much as the learner.
 - a. Learning styles analysis: Before the first day of rotation, have learners complete a brief learning style inventory. Then, during the orientation, briefly discuss it together. Like other types of personality or workstyle inventories, learning style analysis can help preceptors and learners understand each other’s styles and where differences can occur. An open discussion can help prevent misunderstandings and frustrations later during the rotation. It can also help the preceptor plan learning activities for the learner, depending on how he or she learns best.
 - b. Case presentation models (Am J Health Syst Pharm 2012;69:1588-99):
 - i. Traditional case presentation: This strategy prompts the learner to collect and present pertinent findings, evaluate the problem, and make therapeutic recommendations. Preceptors then share their thought process for the best treatment specific to the patient.
 - (a) Potential benefits: Allows self-directed learning and improvement in communication skills of learners
 - (b) Limitations: May not be practical in a busy practice setting and may miss opportunities to delve into the clinical reasoning and problem-solving skills involved in patient cases. To overcome these limitations, preceptors may instruct learners to “think-aloud” their rationale (see the “think-aloud” model for greater detail).

- ii. One-minute preceptor: This strategy maximizes learners' development of critical thinking skills during case discussions. Preceptors use five "microskills" with learners (J Gen Intern Med 2001;16:620-4):
 - (a) "Get a commitment (i.e., ask the learner to articulate his or her own diagnosis or plan)
 - (b) Probe for supporting evidence – evaluate the learner's knowledge or reasoning
 - (c) Teach general rules – teach the learner common 'take-home points' that can be used in future cases, aimed preferably at a learner's area of weakness
 - (d) Reinforce what was done well – provide positive feedback
 - (e) Correct errors – provide constructive feedback with recommendations for improvement."
 - (f) Potential benefits: Is a more efficient and effective method for both preceptors and learners when providing feedback than the traditional case presentations (Acad Med 2004;79:42-9; J Gen Intern Med 2002;17:779-87; Med Teach 2007;29:323-7). Allows learners to recognize areas needing improvement
 - (g) Limitations: Requires training for preceptors and learners before use
- iii. SNAPPS model: This is a learner-centered framework that consists of six steps (Acad Med 2003;78:893-8):
 - (a) "Summarize briefly the history and findings;
 - (b) Narrow the differential to two or three relevant possibilities;
 - (c) Analyze the differential by comparing and contrasting the possibilities;
 - (d) Probe the preceptor by asking questions about uncertainties, difficulties, or alternative approaches;
 - (e) Plan management for the patient's medical issues; and
 - (f) Select a case-related issue for self-directed learning."
 - (g) Potential benefits: Has shown that learners are more likely to communicate uncertainties, ask questions, initiate discussions, and engage in self-directed learning than in traditional case presentations
 - (h) Limitations: Requires training for preceptors and learners before use
- iv. "Think-aloud" model: This strategy requires learners to synthesize and express their process of thinking without providing a structured framework for presentation, contrasting to the one-minute preceptor and SNAPPS models. Learners should be encouraged to think and speak without interruptions, communicate uncertainties, and ask questions as time permits (Nurse Educ Today 2008;28:8-14).
 - (a) Benefits: Can be combined with other case presentation models and integrated into the four major roles of preceptors
 - (b) Limitations: May not be practical in a busy practice setting
- c. Ask-tell-ask: This technique that has been used in patient-provider communication to elicit patients' perspectives and help patients make decisions based on the information, rather than the health care professional just telling the patient what he or she should do. This technique can also be applied to experiential learning, which involves asking learners what they think about a situation, sharing their opinion, and then asking for the learner's opinion once again.
- d. Questioning: This technique of question-and-answer using structured, progressively narrower, open-ended questions can be used to guide learners to the appropriate clinical reasoning process. It can be integrated into the different case presentation models or used to complement assigned readings.
 - i. Potential benefits: Helps learners connect information or when learners digress from the appropriate thinking process

- ii. Limitations: Over-punitive, inappropriate, or punitive use of questioning can lead to learners' frustration and embarrassment. As a result, preceptors must be mindful to balance the questioning to allow learners to demonstrate their knowledge and skills while still challenging them. Furthermore, it is important to allow adequate response time for the learners and not "take over" the discussion.
 - e. Simulation: This is a learning activity meant to serve as a proxy for real-life practice without using real patients or real pharmacies. These activities can be a bridge between learners' didactic learning and real pharmacy practice. More details about using simulations as an adjunct to experiential education can be found in the ACPE "Standards 2016."
 - f. IPPE versus APPE: According to ACPE, the difference between the two lies primarily in the level of learners and responsibilities they will have during the experience. Since the integration of IPPEs into the Pharm.D. curricula, IPPEs have often been used to help learners understand more traditional roles of pharmacists, whereas APPEs are meant to focus more on patient care.
5. Constructing a Course and Lesson Plan
- a. Syllabi for didactic courses and experiential rotations
 - i. All courses and experiential rotations should have syllabi that clearly identify expectations for learners, learning objectives, instruction and assessment methods, policies and guidelines, and other relevant information. Typically, templates are likely to be found at the affiliated school or college of pharmacy.
 - ii. A good syllabus answers learners' questions about the course or rotation, guides learning, and prevents inappropriate behavior because expectations are clearly defined.
 - b. Lesson plans for individual learning lessons: Lesson plans are used by educators and preceptors primarily to help organize and execute a learning activity (or set of learning activities), such as a lecture, a skills lab, or a day or week of a rotation. Lesson plans can also be shared with learners to help guide their learning and promote transparency.
- F. The Four Major Preceptor Roles and Mentoring
- Evidence supporting effective precepting and some instructional techniques for experiential learning has already been shared. This section focuses on the four major preceptor roles (direct instruction, modeling, coaching, and facilitating) and mentoring, which are the primary teaching models in experiential learning.
- 1. Direct Instruction: Although it is rarely a primary role of preceptors in an experiential rotation, direct instruction is important in helping learners establish foundational knowledge and skills. It can occur in the form of topic discussions or review of clinical guidelines, which can benefit even an advanced learner (ASHP 2000:119-31; Am J Health Syst Pharm 2012;69:1588-99).
 - 2. Modeling: Professional socialization is the process whereby a person adopts the attitudes, values, beliefs, and behaviors held by a profession's members. The most influential factor in this process is the role modeling that occurs by preceptors with trainees, both positive and negative.
 - a. Role modeling is usually unintentional on the part of the preceptor. The process of learners' training and learning from preceptors is similar to that of children learning from parents.
 - b. Role modeling should be intentional, with preceptors practicing and interacting with others in a way they would want learners to emulate.
 - 3. Coaching: Nimmo describes coaching as a stage in which the learner is allowed some independence in practice activities, with the preceptor providing feedback and support when needed (ASHP 2000:109-18; Am J Health Syst Pharm 2012;69:1588-99).
 - a. Coaching differs from telling or showing the learner what to do because the learner is allowed to try for himself or herself, usually in the preceptor's presence.
 - b. This model strives for the learner to become independent after proper precepting and coaching.

4. Facilitating: According to Nimmo, preceptors serving as facilitators allow learners to further grow by independently performing patient care activities and self-evaluating their clinical decisions (ASHP 2000:109-18; Am J Health Syst Pharm 2012;69:1588-99).
 - a. Self-evaluation is a learned skill.
 - b. Nimmo describes it in six steps:
 - i. Establish criteria
 - ii. Collect data
 - iii. Compare the data with the criteria
 - iv. Make a judgment
 - v. Make a decision
 - vi. Take appropriate action
5. Mentoring
 - a. As defined in the *Preceptor's Handbook for Pharmacists*, mentoring is “helping others reach their full potential as professionals with the goal of developing practitioners who will pursue and attain excellence as patient care providers, teachers, scientists, managers, and/or leaders. Mentoring is a relationship based on the following:
 - i. Trust and respect
 - ii. Education and nurturing
 - iii. Inspiration to advance the practice of pharmacy and improve patient care
 - iv. Opportunities to grow and develop
 - v. Metamorphosis as engaging in a process of self-reflection, self-assessment, and self-transformation
 - vi. Professional guidance
 - vii. Nomination for awards when success has been achieved”
 - b. Mentoring differs from precepting because precepting is “teaching others the art and science of pharmacy practice in a health care setting with the goal of developing competent practitioners.” Precepting involves:
 - i. A partnership for education
 - ii. Investment of time and energy
 - iii. Negotiation and individualization of learning activities
 - iv. Teamwork
 - v. Coaching
 - vi. Evaluation of performance
 - vii. Professionalism role modeling
 - viii. Guidance
 - c. Some may consider mentoring as descriptive of a learner-pharmacist relationship that is longer term than just a few weeks. Precepting may be most descriptive of the learner-pharmacist relationship for IPPE and APPE.

G. Knowledge and Skill Assessment Techniques

Assessment in education is often the driver for how learners learn. Learners will try to meet or exceed the expectations of the assessment if they are made clear. This section provides greater detail about these assessment techniques and others.

1. Evaluate Assessment Philosophies
 - a. Formative versus summative assessment
 - i. Formative assessment refers to low-stakes assessments that are used primarily to give students feedback on their performance so that they can achieve the learning outcomes and objectives. Formative assessments are not used to assign a grade or make a final judgment on learners’

learning. Learners often get to repeat formative assessments to achieve a higher level of success. An example of formative assessment is a midpoint evaluation of a learner on an APPE where a grade is not given, but the evaluation is used to provide the learner (and possibly the school or college) with feedback on the learner's performance so far.

- ii. On the contrary, summative assessment usually has higher stakes and often determines a final grade or acceptable capstone performance.
- b. Assessment as a learning tool
 - i. This phrase is often used with formative assessment and implies that learners learn from being assessed through high-quality feedback.
 - ii. This strategy is commonly used with mastery and learner-centered education, as well as ABE.
- c. Mastery versus norm-referenced assessment
 - i. Mastery is similar to competence-based grading, where learners are measured against criteria deemed to define competence in any given area rather than being compared with each other.
 - ii. In norm-referenced grading, learners' performances are compared with those of their classmates, and judgments or grades are determined on the basis of high and low performers. Grading on a curve is a type of norm-referenced grading. Bell curves are also used in norm-referenced grading.
 - iii. Mastery lends itself well to pass/no-pass grading, depending on where the pass line is set.
- 2. Design Assessment Strategies
 - a. Instructional alignment is important when designing assessments. Assessments should be designed after developing the learning goals, objectives, and outcomes so that the instruction can be designed to help learners succeed on the assessments.
 - b. The Bloom's cognitive learning level of the outcome or objective should be considered.
 - c. Consider self-assessment, peer assessment, and 360-degree assessment.
 - i. Engaging in self-assessment of their performance and learning can help learners develop better self-awareness (ACPE Standard 4.1) and have greater learning gains.
 - ii. Similarly, when assessing peers' performances, learners can benefit on how to objectively evaluate performance of a certain behavior, such as teamwork on a project, or on an individual SOAP note assignment, and benefit from their peers' feedback about their own performance.
 - iii. 360-degree assessment refers to gathering several assessments from various sources that all observe and interact with the person being assessed. In medicine, for example, medical residents are evaluated by attending physicians, their peers, themselves, nursing and other ancillary health care staff, and patients.
- 3. Specific Assessment Strategies
 - a. Examinations
 - i. Traditional: A few written midterms and a final exam per quarter or semester
 - ii. Group testing: Learners take individual examinations first, then retake the same examination with a group, for a combination score. Research shows that most learners' scores improve when they take a group examination, with greater retention of learning.
 - iii. Computer-based: It is becoming more common for schools to use non-internet databases with examination questions to examine learners with programs such as ExamSoft.
 - iv. Oral: Although time- and labor-intensive, oral examinations are still preferred by some, especially to help prepare learners for the questioning that occurs during APPE and postgraduate training.
 - v. Performance-based: This technique refers to skill testing, such as for communication and physical assessment skills.
 - (a) Many programs use standardized patients to help implement these types of examinations. Some are also known as objective structured clinical examination-type assessments (i.e., where learners move from station to station performing different skills).

- (b) In performance-based assessments as occurring during rotations, the criteria by which learners will be judged must be specific and objective and made explicit. These characteristics can increase consistency between several evaluators or preceptors (interrater reliability).
- b. Other forms of assessment
 - i. Papers: Individual reflection, research, or term papers
 - ii. Projects: Group or individual, on any number of topics
 - iii. Presentations: Group or individual, of projects or papers
 - iv. Interviews: Learners complete interviews of various stakeholders, such as patients, caregivers, providers, or payers, to learn, understand, and develop empathy.
 - v. Reflective journaling: Often used to assess the impact of service learning and other less-quantifiable forms of learning
 - vi. Portfolios: Many programs have learners maintain a portfolio of significant assessments, assignments, and evaluations that demonstrate progress toward and achievement of their competencies and ABOs.
- c. Many techniques are used to measure learners' learning. The best assessments are aligned with learning objectives and desired outcomes, which also motivates learners to learn from them. Instructional and assessment strategies should be well aligned. The content presented earlier should serve as a resource for instructors that can be modified to meet learners' specific needs in various settings and educate and train instructors to meet the needs of optimal pharmacotherapy for the pediatric populations.

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: C**

Answer C is correct; *very low birth weight* classifies premature babies with birth weights of 1000 g to less than 1500 g. Answer A is incorrect; *infant* is used to define children 29 days to less than 12 mo of age. *Neonate* defines children 28 days or younger. Answer B is incorrect; *full term* defines neonates born at 37 weeks' gestation or more. *Premature* is a neonatal terminology to define neonates born at less than 37 weeks' gestation. Answer D is incorrect; pain is perceived by patients of all ages, including newborns. Therefore, pain assessment should be part of the routine assessments of pediatric patients.

2. Answer: A

Answer A is correct; the calculation was performed incorrectly. The patient should be instructed to obtain up to 10 mL of the 3-mg/mL simplified lansoprazole solution to provide the prescribed lansoprazole dose (1.5 mg/kg = 30 mg total). Answer B is incorrect; the prescribed lansoprazole dose is within the recommended maximum daily dose. Answer C is incorrect; lansoprazole is available as a simplified lansoprazole solution. Answer D is incorrect; no trailing zeros were used in the case.

3. Answer: D

Answer D is correct; an incentive-based Best Pharmaceuticals for Children Act was implemented in 2002, extending the FDAMA, including the provision from the 1997 FDAMA offering an additional 6 months of patent exclusivity for on-patent drugs being tested for pediatric use, thereby encouraging industry to conduct pediatric studies for branded products labeled only for adults. Answer A is incorrect; the Pediatric Rule, issued in 1994, permitted manufacturers to label drugs for pediatric use according to 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. Answer B is incorrect; the Orphan Drug Act supports the development of needed treatment of rare diseases with an occurrence of 200,000 people or fewer in the United States, such as inborn errors of metabolism. Answer C is incorrect; the Pediatric Research Equity Act of 2003 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-benefit in pediatric patients.

4. Answer: C

Answer C is correct; behavioral and educational approaches such as motivational interviewing have received the most emphasis in studies regarding chronic diseases such as pediatric asthma and diabetes. Answer A is incorrect; medication adherence should be assessed. Answer B is incorrect; maximum doses are often adult doses; however, such dosing should be verified using a pediatric dosing reference. Answer D is incorrect; sensitive issues that are more mature or adult in nature affecting health, including alcohol, tobacco, illicit drug use, sexual activity, and psychosocial concerns, should be considered.

5. Answer: C

Answer C is correct; general tips recommended for communicating with children and adolescents include giving them ample time to respond to questions. Answer A is incorrect; the pharmacist should sit at or below the child's eye level. Answer B is incorrect; a normal tone of voice should be used. Answer D is incorrect; differences in culture that may affect a person's likelihood of maintaining eye contact and interest in self-care should be considered.

6. Answer: A

Answer A, determine who will be administering the medication to children, is correct. Medication is often administered at school or by a grandparent, or it may be administered at another house if the parents do not live together. If the person accompanying the child to the visit is not the only one to administer the medication, the adult who is present at the visit should be educated on the importance of providing all information to everyone who will be responsible for giving the child's medication. Answer B is incorrect. Encourage them to provide their child with some autonomy, when appropriate. Answer C is incorrect. Parent-friendly medication information handouts should be presented in the caregiver's primary language, which in this case is Spanish. Lexicomp online provides pediatric-specific patient education handouts in 18 languages. Answer D is incorrect. Respond respectfully about any misconceptions or

fears they may express. Written information dispensed with prescriptions is often not phrased with a child in mind and can be frightening and confusing to parents or caregivers.

7. Answer: A

Answer A, Standard 6: College or School Vision, Mission, and Goals, is correct. “The college or school publishes statements of its vision, mission, and goals.” Regarding Standard 6.3, Education, scholarship, service, and practice, “The statements address the college or school’s commitment to professional education, research and scholarship, professional and community service, pharmacy practice and continuing professional development.” Answer B, Standard 12: Pre-APPE Curriculum, is incorrect. “The Pre-APPE curriculum must provide a rigorous foundation in the biomedical, pharmaceutical, social/administrative/behavioral and clinical sciences and incorporate Introductory Pharmacy Practice Experience (IPPE) in order to prepare students for Advanced Pharmacy Practice Experience (APPE).” Answer C, Standard 19: Faculty and Staff – Qualitative Factors, is incorrect. “Faculty and staff must have academic and professional credentials and expertise commensurate with their responsibilities to the professional program and their academic rank.” Answer D, Standard 20: Preceptors, is incorrect. “The college or school must have a sufficient number of preceptors (practice faculty or external practitioners) to effectively deliver and evaluate students in the experiential component of the curriculum. Preceptors must have professional credentials and expertise commensurate with their responsibilities to the professional program.”

8. Answer: B

Answer B is correct; in Figure 7, “explain” is associated with comprehension. Answer A is incorrect; in Figure 7, “define” is associated with knowledge. Answer C is incorrect; in Figure 7, “prioritize” is associated with analysis. Answer D is incorrect; in Figure 7, “recommend” is associated with evaluation.

9. Answer: B

Answer B is correct; the one-minute preceptor maximizes learners’ development of critical thinking skills during case discussions using the five “microskills”: get commitment, probe for supporting evidence, teach general rules, reinforce what was done well, and correct errors. The model is more efficient and effective

in providing more specific and constructive feedback than are traditional case presentations. Answer A is incorrect; the traditional case presentation prompts the learner to collect and present pertinent findings, evaluate the problem, and make therapeutic recommendations. Preceptors then share their thought process for the best treatment specific to the patient. Answer C is incorrect; the SNAPPS model is a learner-centered framework that consists of six steps: summarize briefly the history and findings; narrow the differential to two or three relevant possibilities; analyze the differential by comparing and contrasting the possibilities; probe the preceptor by asking questions about uncertainties, difficulties, or alternative approaches; plan management for the patient’s medical issues; and select a case-related issue for self-directed learning. Although learners are more likely to communicate uncertainties, ask questions, initiate discussions, and engage in self-directed learning in the SNAPPS model than in the traditional case presentations, the model may not be most efficient at the beginning of rotation because it requires training for both preceptors and learners before use. Answer D is incorrect; the think-aloud model requires learners to synthesize and express their process of thinking without providing a structured framework for presentation, in contrast to the one-minute preceptor and SNAPPS models.

10. Answer: D

Answer D is correct; engaging in self-assessment of performance and learning can help learners develop better self-awareness (ACPE Standard 4.1) and have greater learning gains. Answer A is incorrect; 360-degree assessment refers to gathering several assessments from various sources that all observe and interact with the person being assessed. Answer B is incorrect; when assessing peers’ performances, learners can benefit on how to objectively evaluate the performance of a certain behavior, such as teamwork on a project, or on an individual SOAP note assignment, and benefit from their peers’ feedback about their own performance. Answer C is incorrect; reflective journaling is often used to assess the impact of service learning and other, less quantifiable forms of learning.

BIOSTATISTICS

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BIOSTATISTICS

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Learning Objectives

1. Describe, calculate, and interpret descriptive and inferential statistics.
2. Identify different types of data to determine an appropriate type of statistical test on the basis of the sample distribution, data type, and study design.
3. Describe, calculate, and interpret different types of measures of central tendency, data spread, and standard error of the mean.
4. Describe hypothesis testing, decision errors, p values, and confidence intervals.
5. Interpret the results of the most appropriate statistical test chosen on the basis of a given scenario.

Abbreviations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
IQR	Interquartile range
SEM	Standard error of the mean

Self-Assessment Questions

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

1. To compare the pain control offered by two different analgesics in pediatric patients, the authors selected the Wong-Baker FACES pain rating scale as the primary end point. Before beginning the clinical trial, the authors sought to validate this ordinal scale by showing a correlation with a previously validated visual analog scale. Which statistical test is most appropriate to assess whether a correlation exists between these two measures?
 - A. Pearson correlation.
 - B. Analysis of variance (ANOVA).
 - C. Spearman rank correlation.
 - D. Regression analysis.
 2. Which statement best describes why journals prefer that investigators report confidence intervals (CIs) versus p values when comparing groups?
 - A. The p value reports neither the statistical significance nor an estimate of the magnitude of the difference observed between groups.
 - B. The CI reports the observation of statistical significance as well as an estimate of the magnitude of the difference between groups.
 - C. Although the CI does not show whether statistical significance was observed, it does report an estimate of the magnitude of the difference between groups.
 - D. The p value reports an estimate of the magnitude of the difference observed between groups, but it does not show whether the investigators observed a statistical significance.
- Questions 3 and 4 pertain to the following case.*
 Investigators have chosen the Wong-Baker FACES pain rating scale to show that a new analgesic works better than placebo in children. The authors plan to randomize subjects to two separate groups.
3. Which is the most appropriate statistical test?
 - A. Student t-test.
 - B. Paired Student t-test.
 - C. Wilcoxon rank sum.
 - D. Pearson correlation.
 4. While designing this study, the investigators realized that they did not have a large enough budget to support the sample size estimated. Which statistical test is best if they decide to use a paired design to decrease the number of subjects required while maintaining similar power?
 - A. Paired Student t-test.
 - B. Wilcoxon rank sum.
 - C. Wilcoxon signed rank.
 - D. McNemar test.
- Questions 5–10 pertain to the following case.*
 Drug X has just received FDA (U.S. Food and Drug Administration) approval for lowering the low-density lipoprotein cholesterol (LDL) in adults. You would like to design a clinical trial to see whether the new drug is effective in your pediatric population. To gather some preliminary evidence, you have measured the LDL in children who have been treated with drug X at baseline and after 3 months of therapy and observed the data to be normally distributed.

5. Which descriptive statistics would be best to summarize the baseline LDL in your subjects?
 - A. Median and interquartile range (IQR).
 - B. Mean and standard deviation (SD).
 - C. Mean and standard error (SE).
 - D. Mode and range.
6. Your next objective is to compare the baseline LDL with the LDL collected after administering drug X for 3 months. Which statistical test would be best if the goal were to maximize the likelihood of avoiding a type II error?
 - A. Paired Student t-test.
 - B. Wilcoxon signed rank.
 - C. ANOVA.
 - D. Chi-square test.
7. After analyzing your data, you have determined that you have enough preliminary evidence to warrant designing a clinical trial at your practice. Considering your limited budget, you would like to do everything possible to decrease your sample size estimate while maintaining the same power or likelihood to detect a difference after 1 year of treatment. Which is best to achieve this goal?
 - A. Decrease the α .
 - B. Increase the delta.
 - C. Choose an outcome measure that has increased variability compared with the LDL.
 - D. Choose a parallel instead of a paired study design.
8. After collecting data comparing the ability of drugs X and Y to decrease the LDL in two separate groups of children after 1 year of treatment, you are prepared to present your results at a scientific meeting. The abstract submission guidelines for this meeting limit you to 250 words. Which is best to report the difference between groups?
 - A. The difference between groups in LDL reduction from baseline after 1 year of treatment and the 95% CI of this estimate.
 - B. The change in LDL compared with baseline after 1 year of treatment for subjects treated with drugs X and Y and the 95% CI of each of these estimates.
 - C. The mean LDL in each group after 1 year of treatment, together with 95% CI of this estimate.
 - D. The difference between groups in LDL reduction from baseline after 1 year of treatment and the p value of this estimate.
9. Your results show that compared with drug Y use, the use of drug X decreases the LDL more in children after 1 year of treatment, and you would like to determine whether this effect holds up after considering the influence of one or more covariates. Which would best allow you to achieve this aim?
 - A. Analysis of covariance (ANCOVA).
 - B. Mann-Whitney U test.
 - C. Student t-test.
 - D. ANOVA.
10. Now that there is enough published evidence showing that drug X is effective in decreasing the LDL in your pediatric population, you are asked to participate in a multicenter clinical trial to determine whether drug X decreases time to mortality. Which statistical test would be most appropriate to achieve this aim?
 - A. Repeated-measures ANOVA.
 - B. Chi-square test.
 - C. Kruskal-Wallis test.
 - D. Cox proportional hazards model.
11. Using a regression model, investigators were able to show that children with cancer had an odds ratio (OR) of 1.5 (95% CI, 1.2–2.0) of experiencing an experimental outcome compared with children without cancer. Which is the best interpretation of the reported results?
 - A. Children with cancer had 1.5 times the odds of having the outcome compared with children without cancer, but the difference was not statistically significant.
 - B. Children with cancer had 1.5 times the odds of having the outcome compared with children without cancer, and the difference was statistically significant.
 - C. Children without cancer had 1.5 times the odds of having the outcome compared with children with cancer, and the difference was statistically significant.

- D. Without a p value, the reader cannot discern whether the difference between groups was statistically significant.
12. A randomized controlled trial was performed to determine whether there was a difference in outcome between drug A and drug B in children. The 100 subjects who completed the trial were divided equally between the two treatment groups. Thirty children who received drug A experienced the outcome, whereas only 20 children who received drug B experienced the outcome. Which statement is the best estimate of the relative risk comparing the outcome in children who received drug A with the outcome in children who received drug B?
- 0.44.
 - 1.5.
 - 2.25.
 - 15.
13. To increase the power of their analysis, investigators must decide which type of data to collect that can meet the criteria of a paired Student t-test. Which type of data would be best?
- Continuous.
 - Nominal.
 - Ordinal.
 - Discrete.
14. If an author's goal is to describe the center and variance of a continuous variable that is normally distributed, use of which pair of statistics would be best?
- Mean and SE.
 - Median and SD.
 - Mean and SD.
 - Median and IQR.
15. An investigator is submitting a 250-word abstract to a peer-reviewed pharmacy practice meeting. Which measure would best allow a reader to discern whether a statistically and clinically significant difference in lowering blood pressure exists between the groups of subjects that are being compared in the clinical trial?
- p value.
 - Median.
 - 95% CI.
 - Variance.
16. Which statistical test would be most appropriate if an investigator were comparing the results of three separate groups of subjects when the results have been measured on an ordinal scale?
- Kruskal-Wallis.
 - Student t-test.
 - ANOVA.
 - Friedman ANOVA.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:
Domain 3: Information Management, Research, and Education; Task(s): 3.3, 3.4

I. BIostatISTICS: AN IMPORTANT PRACTICE TOOL

- A. Allows us to classify, summarize, and analyze data
- B. Enables investigators to summarize data, determine the likelihood that a treatment or procedure affects a group of patients, and estimate the effect size
- C. Useful in helping us determine whether the results of a study can be applied to our practice
- D. Why Pharmacists Need to Know Statistics
- E. As Statistics Pertains to Most of You
 - 1. Pediatric Pharmacy Specialty Examination content outline, Domain 3: Information Management, Research and Education (17%)
 - 2. Task statements:
 - a. 3.3. Contribute to the pediatric body of knowledge (e.g., conduct or participate in research, deliver presentations, participate as a peer reviewer, publish)
 - b. 3.4. Retrieve and interpret biomedical literature with respect to study methods, statistical analysis, study results, and applicability to pediatric pharmacy practice
- F. Examples of Online Statistical and Study Design Tools
 - 1. www.graphpad.com/quickcalcs/
 - 2. <http://statpages.org/>

II. TYPES OF VARIABLES/DATA

- A. Definition of Random Variables: A variable is any characteristic, number, or quantity that can be measured or counted; a random variable is a variable for which the value cannot be anticipated with certainty before the study or experiment is carried out.
- B. Two Types of Random Variables
 - 1. Qualitative
 - 2. Quantitative
- C. Qualitative Variables
 - 1. Can take only a few values within a given range
 - 2. Often called categorical variables
 - 3. Nominal: Classified into groups in an unordered manner and with no indication of relative severity (e.g., mortality [dead or alive], disease presence [yes or no], race, marital status)
 - 4. Ordinal: Ranked in a specific order but with no consistent level of magnitude of difference between ranks (e.g., NYHA [New York Heart Association] functional class describes the functional status of patients with heart failure, and subjects are classified in increasing order of symptoms: I, II, III, IV; Likert-type scales [strongly agree {SA}, agree {A}, neutral {N}, disagree {D}, strongly disagree {SD}; disease stages [A, B, C, D])
 - 5. Common error: Measure of central tendency – In most cases, means and standard deviations (SDs) should not be reported with ordinal data. What is a common incorrect use of means and SDs to show ordinal data?

D. Quantitative Variables

1. Discrete quantitative variables can take on specific numeric values (1, 2, 3, 4, etc.), rather than any value in an interval. These numeric values have a clear quantitative value (number of hospitalizations, number of pregnancies).
2. Quantitative continuous variables can take on any value within a given range.
 - a. Interval: Data are ranked in a specific order with a consistent change in magnitude between units; the zero point is arbitrary (e.g., degrees Fahrenheit).
 - b. Ratio: Like “interval” but with an absolute zero (e.g., degrees Kelvin, heart rate, blood pressure, time, distance)

III. TYPES OF STATISTICS

A. Descriptive Statistics: Used to summarize and describe data that are collected or generated in research studies. This is done both visually and numerically.

1. Visual methods of describing data
 - a. Frequency distribution
 - b. Histogram
 - c. Scatterplot
 - d. Boxplot
2. Numerical methods of describing data: Measures of central tendency
 - a. Arithmetic mean (i.e., average)
 - i. Sum of all values divided by the total number of values
 - ii. Should generally be used only for continuous and normally distributed data
 - iii. Very sensitive to outliers and tend toward the tail, which has the outliers
 - iv. Most commonly used and most well understood measure of central tendency
 - v. Geometric mean
 - b. Median
 - i. Midpoint of the values when placed in order from highest to lowest. Half of the observations are above and half are below. When the number of observations is even, it is the mean of the two middle values.
 - ii. Also called the 50th percentile
 - iii. Can be used for ordinal or continuous data (especially good for skewed populations)
 - iv. Insensitive to outliers
 - c. Mode
 - i. Most common value in a distribution
 - ii. Can be used for nominal, ordinal, or continuous data
 - iii. Sometimes, there may be more than one mode (e.g., bimodal, trimodal).
 - iv. Does not help describe meaningful distributions with a large range of values, each of which occurs infrequently
3. Numerical methods of describing data: Measures of data spread or variability
 - a. Standard deviation
 - i. Measure of the variability about the mean; most common measure used to describe the spread of data
 - ii. Square root of the variance (average squared difference of each observation from the mean); returns variance back to original units (non-squared)
 - iii. Appropriately applied only to continuous data that are normally or near-normally distributed or that can be transformed to be normally distributed

- iv. By the empirical rule for normal distributions, 68% of the sample values are found within 1 SD, 95% are found within 2 SDs, and 99% are found within 3 SDs.
- v. The coefficient of variation relates the mean and the SD ($SD/\text{mean} \times 100\%$).
- vi. Knowledge of the mean and SD allows the reader to re-create the distribution of data.
- b. Range
 - i. Difference between the smallest and largest value in a data set
 - ii. Easy to compute (simple subtraction) but not very informative by itself
 - iii. Size of range is very sensitive to outliers.
 - iv. Often reported as the actual values rather than the difference between the two extreme values
- c. Percentiles
 - i. The point (value) in a distribution below which a certain percentage of values lie
 - ii. The 50th percentile lies at a point at which 50% of the other values in the group are smaller; 50th percentile also represents the median of the data.
 - iii. Unlike with the mean, normal distribution need not be assumed.
 - iv. The IQR describes the middle 50% of values ($IQR = 25\text{th} - 75\text{th percentile}$).
- 4. Presenting data using only measures of central tendency can be misleading without some idea of data spread. Studies that report only medians or means without their accompanying measures of data spread should be closely scrutinized. Which measures of spread should be used with means and medians?
- 5. Probabilities versus proportions versus percentage: Probabilities and proportions are calculated the same way, and both can be expressed as a percentage; however, the term *proportions* refers to preexisting information, and *probabilities* refers to the future.
- B. Inferential Statistics
 - 1. Conclusions or generalizations made about a population (large group) from the study of a sample of that population
 - 2. Used to test hypothesis and make estimations based on samples of a population
 - 3. Choosing and evaluating statistical methods depend, in part, on the type of data used.
 - 4. An educated statement about an unknown population is commonly called an inference in statistics.
 - 5. Statistical inference can be made by estimation or hypothesis testing.

IV. POPULATION DISTRIBUTIONS

- A. Discrete Distributions
 - 1. Binomial distribution – There are two possible outcomes; the probability of obtaining either outcome is known, and you want to know the chance of observing a certain number of successes in a certain number of trials.
 - 2. Poisson distribution – Counting events in a certain period of observation: The average number of counts is known, and you want to know the likelihood of observing a various number of events.
- B. Continuous Distribution: The Normal (Gaussian) Distribution
 - 1. Most common model for population distributions
 - 2. Symmetric or “bell-shaped” frequency distribution
 - 3. When measuring a random variable in a large-enough sample of any population, some values will occur more often than others.
 - 4. Determining whether there is a normal distribution
 - a. Visually inspect the distribution looking for symmetry and the characteristic bell-shaped curve. To visually inspect the frequency distribution and histograms, you will need these data.
 - b. Median and mean will be about the same; this is the easiest and most practical method.

- c. There are formal tests, including the Kolmogorov-Smirnov test.
- d. Unfortunately, most papers do not present all the data, do not include a histogram, or do not report both the mean and the median: The onus is on the authors if the editors and readers question the reporting methods.
- 5. Normally distributed data are termed *parametric* because the parameters, mean and SD, completely define the distribution of the data.
- 6. Probability: The likelihood that any one event will occur given all the possible outcomes
- 7. Estimation and sampling variability: SD versus standard error of the mean (SEM)
 - a. We rarely have enough resources to sample an entire population; therefore, we take samples of a population and make inferences about a population parameter.
 - b. Multiple samples (even if the same number of observations per sample) from a single population will give slightly different estimates.
 - c. The distribution of means from random samples approximates a normal distribution.
 - i. The mean of the distribution of means is the unknown population mean (μ).
 - ii. The SEM is the estimate of the SD of the distribution of means.
 - iii. Like any normal distribution, 95% of the sample means lie within ± 2 SEM of the population mean; this is true even if the sample data set from which the means were estimated is not normally distributed (central limit theorem).
 - d. The SEM is estimated using a single sample by dividing the SD by the square root of the sample size (n).
 - e. The SEM quantifies uncertainty in the estimate of the true population mean, not variability in the sample.
 - f. SEM is important for hypothesis testing and estimation of the 95% CI.
 - g. Common error: Reporting SEM versus SD, which makes the distribution of the results look tighter or less “variable,” especially when reported graphically.

V. CONFIDENCE INTERVALS

A. Commonly Reported as a Way to Estimate a Population Parameter

- 1. In the medical literature, 95% CIs are the most commonly reported CIs. The CI represents the range of values that the true value lies within. In some cases, 90% or 99% CIs are reported. Why are 95% CIs most often reported?
- 2. Example:
 - a. Assume a baseline birth weight in a group ($n=51$) with a mean $\pm$ SD of 1.18 ± 0.4 kg.
 - b. 95% CI is about equal to the mean $\pm 1.96 \times$ SEM (or $2 \times$ SEM). In reality, it depends on the distribution being used and is somewhat more complicated.
 - c. What is the 95% CI? The 95% CI is calculated to be (1.07, 1.29), meaning there is 95% certainty that the true mean of the entire population studied will be 1.07–1.29 kg.
 - d. What is the 90% CI? The 90% CI is calculated to be (1.09, 1.27). The 95% CI will always be wider than the 90% CI for any given sample. Therefore, the wider the CI, the more likely it is to encompass the true population mean.
- 3. The differences between the SD, SEM, and CI should be noted when interpreting the literature because their interpretation is often confused. Although CIs are commonly confused with SDs, the information each provides is quite different and has to be assessed correctly.

- B. CIs Can Be Calculated for Any Sample Estimate: In addition to descriptive data, CIs are commonly reported when publishing the results of comparative studies, including point estimates of differences between groups and estimates derived from categorical data such as risk, risk differences, and risk ratios.

VI. HYPOTHESIS TESTING

A. Null and Alternative Hypotheses for Superiority Trials

1. Null hypothesis (H_0): The hypothesis an investigator is trying to disprove or reject; when comparing groups, statement of no difference between groups being compared (treatment A = treatment B)
2. Alternative hypothesis (H_a): Opposite of null hypothesis; when comparing groups, statement of a difference between groups being compared (treatment A $\neq$ treatment B)
3. The structure or the manner in which the hypothesis is written dictates which statistical test is used (e.g., for a two-sample Student t-test, the H_0 : mean 1 = mean 2).
4. Used to help determine whether any observed differences between groups can be explained by chance
5. Tests for statistical significance (hypothesis testing) determine whether the data are consistent with the H_0 (no difference).
6. The results of the hypothesis testing will indicate whether enough evidence exists for the H_0 to be rejected.
 - a. If H_0 is rejected: Statistically significant difference between groups (unlikely to be attributable to chance)
 - b. If H_0 is not rejected: No statistically significant difference between groups (any apparent differences may be attributable to chance). Note that we are not concluding that the treatments are equal.
7. Types of hypothesis testing: There are numerous other examples of situations these procedures could be applied to as shown in the Table 1.

Table 1. Types of Hypothesis Testing

	Question	Hypothesis	Method
Nondirectional			
Difference	Are the means different?	H_0 : Mean1 = Mean2 H_a : Mean1 $\neq$ Mean2 or H_0 : Mean ₁ - Mean ₂ = 0 H_a : Mean ₁ - Mean ₂ $\neq$ 0	Traditional 2-sided t-test Confidence intervals
Equivalence	Are the means practically equivalent?	H_0 : Mean1 - Mean2 $\geq \Delta$ H_a : Mean ₁ - Mean ₂ $< \Delta$	Two 1-sided t-test (TOST) procedure Confidence intervals
Directional			
Superiority	Is mean 1 > mean 2? (or some other similarly worded question)	H_0 : Mean1 $\leq$ Mean2 H_a : Mean1 > Mean2 or H_0 : Mean ₁ - Mean ₂ $\leq$ 0 H_a : Mean ₁ - Mean ₂ > 0	Traditional 1-sided t-test Confidence intervals
Noninferiority	Is mean 1 no more than a certain amount lower than mean 2?	H_0 : Mean1 - Mean2 $\geq \Delta$ H_a : Mean ₁ - Mean ₂ < Δ	Confidence intervals

Δ = equivalence or noninferiority margin; H_0 = null hypothesis; H_a = alternative hypothesis.

B. Determining What Is Sufficient Evidence to Reject H_0

1. Set the a priori significance level (α), and generate the decision rule.
2. Developed after the research question has been stated in hypothesis form
3. Used to determine the level of acceptable error caused by a false positive (also known as level of significance)
 - a. Convention: A priori α is most often 0.05.
 - b. *Critical value* is calculated, capturing how extreme the sample data must be to reject H_0 .

C. Perform the Experiment and Estimate the Test Statistic

1. A test statistic is calculated from the observed data in the study and compared with the critical value.
2. Depending on this test statistic's value, H_0 is "not rejected" (often called fail to reject) or rejected.
3. A p value is the probability of obtaining a test statistic as extreme, or more extreme, than the one actually obtained; it is the likelihood of getting the results you did, or something more extreme given that the null hypothesis is true (no difference between groups).
4. In general, the test statistic and critical value are not presented in the literature; instead, a p value is reported and compared with an a priori α value to assess statistical significance.

D. CIs Instead of Hypothesis Testing

1. Hypothesis testing and calculation of p values tell us (ideally) whether there is a statistically significant difference between groups, but nothing about the magnitude of the difference.
2. CIs help us determine the importance of a finding or findings, which we can apply to a given situation.
3. CIs give us an idea of the magnitude of the difference between groups and the statistical significance.
4. CIs are a range of data, together with a point estimate of the difference.
5. Wide CIs
 - a. Many results are possible, either larger or smaller than the point estimate provided by the study.
 - b. All values contained in the CI are statistically plausible.
6. If the estimate is the difference between two continuous variables: A CI that includes zero (no difference between two variables) can be interpreted as not statistically significant (a p value of 0.05 or greater). There is no need to show both the 95% CI and the p value.
7. The interpretation of CIs for odds ratios and relative risks is somewhat different. In that case, a value of 1 indicates no difference in risk, and if the CI includes 1, there is no statistical difference. (See the discussion of case-control/cohort studies in other sections for how to interpret CIs for odds ratios and relative risks.)
8. There is no need to report both the 95% CI and the p value.

VII. DECISION ERRORS WHEN COMPARING GROUPS

Table 2. Summary of Decision Errors

Test Result	Underlying "Truth" or Reality in Sampled Population	
	H_0 Is True (no difference)	H_0 Is False (difference)
Accept H_0 (failed to find a difference)	No error (correct decision)	Type II error (beta error)
Reject H_0 (conclude there is a difference)	Type I error (alpha error)	No error (correct decision)

H_0 = null hypothesis.

A. Type I Error: The probability or likelihood of making this error is defined as the significance level α .

1. Convention is to set α to 0.05, effectively meaning that, 1 in 20 times, a type I error will occur when the H_0 is rejected, or that 5.0% of the time, a researcher will conclude that there is a statistically significant difference between groups in the sampled population when one does not actually exist.
2. The calculated chance that a type I error has occurred is called the "p value."
3. The p value tells us the likelihood of obtaining a given (or a more extreme) test result if the H_0 is true. When the α level is set a priori, H_0 is rejected when p is less than α . The p value tells us the probability of being wrong when we conclude that a true difference exists in the sampled population (type I error).

4. A lower p value does not mean the result is more important or clinically meaningful, but only that it is statistically significant and not likely attributable to chance. CIs are much more informative when applying the results to our clinical practice.
- B. Type II Error: The probability or likelihood of making this error is termed β .
1. Concluding that no difference exists in the sampled population when a difference truly exists in the population from which the sample was obtained
 2. It has become conventional to set β between 0.20 and 0.10, which effectively means that an investigator will fail to conclude that a statistically significant difference exists between sampled groups when one actually does exist 20% and 10% of the time, respectively: We are much more tolerant of a type II versus a type I error because reporting a difference is more likely to change the way we practice.
- C. Power = $(1 - \beta)$
1. The probability or likelihood of correctly rejecting the H_0 when a difference between groups in the sampled population is present
 2. Dependent on the following factors:
 - a. Predetermined α : A smaller α or risk of error you will tolerate when rejecting H_0 results in a decrease in power
 - b. Sample size: An increase in sample size results in an increase in power.
 - c. The delta or size of the difference between the outcomes you wish to detect: An increase in delta results in an increase in power, or the larger the difference you have designed your study to detect, the higher the power. Delta is the size of difference you have determined to be clinically significant before the study begins.
 - d. The variability in the outcomes that are being measured: An increase in variability results in a decrease in power. Variability is estimated from previous data or published results.
 - e. Poor study design may negatively influence power.
 - f. Failure to select the most appropriate statistical test may decrease power (e.g., using a nonparametric test when a parametric test is appropriate; using a non-paired test when a paired test is appropriate).
 3. Sample size calculation and statistical power analysis
 - a. Increase in sample size results in a decrease in type I and type II errors; unfortunately, the budget often restricts the number of subjects we can recruit for a study.
 - b. Sample size estimates should be performed in all studies a priori (before they begin).
 - c. Important factors for estimating an appropriate sample size
 - i. Acceptable β or type II error rate (usually 0.10–0.20)
 - ii. Selecting an a priori difference (delta) in study outcomes that is clinically relevant
 - iii. The estimated variability in the outcome measured
 - iv. Acceptable α or type I error rate (usually 0.05)
 - v. Statistical test used to test the hypothesis for the primary end point
 4. Statistical significance versus clinical significance
 - a. The size of the p value is not related to the clinical importance of the result. Smaller values mean only that “chance” is less likely to explain the observed differences.
 - b. Statistically significant does not necessarily mean clinically significant.
 - c. Lack of statistical significance does not mean that results are not clinically important: Consider factors that could have affected the power such as sample size, delta, and observed variability.

d. Example:

Table 3. Four Studies Are Carried Out to Test the Response Rate to a New Drug Compared with That of a Standard Drug

Study	New Drug Response Rate (%)	Standard Response Rate (%)	Difference in % Responding		
			p value	Point Estimate (%)	95% CI
1	480/800 (60)	416/800 (52)	0.001	8	3% to 13%
2	15/25 (60)	13/25 (52)	0.57	8	−19% to 35%
3	15/25 (60)	9/25 (36)	0.09	24	−3% to 51%
4	240/400 (60)	144/400 (36)	< 0.0001	24	17% to 31%

- e. Which study (or studies) observed a statistically significant difference in response rate?
- f. If the smallest change in response rate thought to be clinically significant is 15%, which of these trials may be convincing enough to change your practice?

VIII. CHOOSING A STATISTICAL TEST WHEN COMPARING GROUPS

- A. The ability to decide between the more common statistical tests used to determine whether a difference exists between groups is necessary for interpreting the medical literature and performing research.
- B. Choosing the Appropriate Statistical Test Depends on
 1. Type of data: Nominal, ordinal, or continuous
 2. Distribution or spread of data: Some tests require that certain criteria be met concerning the data distribution.
 3. Number of groups: Certain tests are not statistically valid when comparing more than two groups.
 4. Study design: Groups may be independent (e.g., parallel) or related (e.g., matched or crossover).
 5. Presence of confounding variables
 6. One-tailed versus two-tailed tests
 7. Parametric versus nonparametric tests
 - a. Parametric tests assume that
 - i. Data are randomly sampled from a parent population with a normal or near-normal distribution; methods to determine this include looking at the data distribution, comparing the mean and median, or using statistical tests
 - ii. Measured (dependent) data are continuous and on either an interval or a ratio scale
 - iii. Homogeneity of data variance between groups being compared (homoscedasticity)
 - b. Nonparametric tests are used when data do not meet the parametric test criteria (e.g., data are not normally distributed, the distribution cannot be discerned, or the data measured are nominal or ordinal).

8. Examples of representative statistical tests (Figure 1)

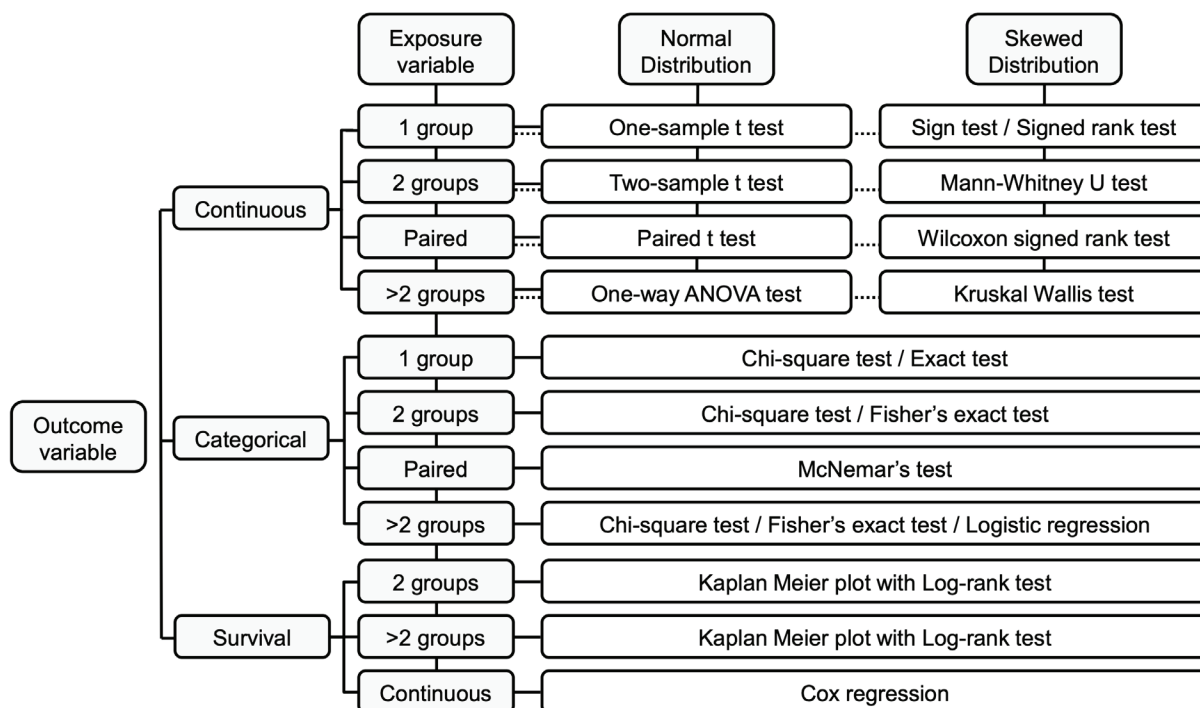


Figure 1. Flowchart of representative statistical tests.

Information from: Baker WE, Sowinski KM. Biostatistics and study designs: fundamentals of design and interpretation. In: Updates in Therapeutics®: Cardiology Pharmacy Preparatory Review Course. American College of Clinical Pharmacy, 2018.

C. Parametric Tests

1. Student t-test: A statistical hypothesis test for comparing two groups that follow a Student t-test distribution

- a. One-sample test: Compares the mean of the study sample with the population mean

Group 1	Known population mean

- b. Independent or unpaired samples t-test: Compares the means of two independent samples

Group 1	Group 2

- i. Equal variance test: Populations being compared should have the same variance.
 - (a) A rule of thumb for variances: If the ratio of a larger variance to a smaller variance is greater than 2, most would conclude that the variances are unequal.
 - (b) There are formal ways to test for differences in variances (e.g., the F-test). Adjustments can be made for cases of unequal variance; in most cases, the Student t-test is not particularly sensitive to inequality of variance.
- ii. Unequal variance test: There are also tests that adjust for unequal variance.

- c. Paired t-test: Compares the means of paired samples or repeated measures

Group 1	
Measurement 1	Measurement 2

- d. Common error: Use of several t-tests versus ANOVA when more than two groups
2. ANOVA: A more generalized version of the t-test that can apply to more than two groups
- a. One-way ANOVA: Compares the means of three or more independent groups: Sometimes called single-factor ANOVA

Group 1	Group 2	Group 3

- b. Two-way ANOVA: Compares the means of three or more independent groups for two categorically independent variables

Young groups	Group 1	Group 2	Group 3
Old groups	Group 1	Group 2	Group 3

- c. Repeated-measures ANOVA: Compares the means of three or more related groups

	Related Measurements		
Group 1	Measurement 1	Measurement 2	Measurement 3

- d. Several more complex factorial ANOVA tests are available.
- e. It is important to remember that these tests determine whether a difference exists between the groups being compared but that they do not identify which specific groups are different; to accomplish this without making a statistical error, investigators use several different post hoc tests such as the Tukey, Bonferroni, Scheffé, or Newman-Keuls.
3. ANCOVA: Compares the means of three or more independent groups while statistically controlling for another continuous independent variable (covariate) that may be negatively influencing (confounding) your results

D. Nonparametric Tests

1. Independent samples
 - a. The Wilcoxon rank sum test and the Mann-Whitney *U* test are used to compare two independent samples; both are related to the Student t-test.
 - b. The Kruskal-Wallis test is used to compare three or more independent groups and is related to the one-way ANOVA test. As with other tests that compare more than two groups, post hoc testing is required to determine which specific groups are different.
2. Matched or paired samples
 - a. Sign test and Wilcoxon signed rank test are used to compare two matched or paired samples and are related to a paired t-test.
 - b. Friedman ANOVA by ranks is used to compare three or more matched or paired groups and is related to the repeated-measures ANOVA test.
3. Nonparametric tests are also used to compare groups when the dependent variable is continuous if other assumptions for the parametric tests are not met.

E. Nominal Dependent Data

1. Chi-square (χ^2) test: A nonparametric test used to compare expected and observed proportions between two or more groups
 - a. Test of independence: Used to test if there is a significant association between two categorical variables from a single population
 - b. Goodness-of-fit test: A single-sample nonparametric test used to determine whether the distribution of participants follows a known or hypothesized distribution
 - c. Commonly represented by contingency tables (Table 4)
2. Fisher exact test: Specialized version of the chi-square test for small groups (cells) containing less than five predicted observations
3. McNemar: Used to compare paired samples such as a before and after study, or when two treatments are given to matched subjects
4. Mantel-Haenszel: Used to control for the influence of confounders when comparing dichotomous outcomes (e.g., stratifying into age groups or other potential risks factors related to the outcome of interest)

Table 4. Example of a 2×2 Contingency Table

	Outcome Achieved	Outcome Not Achieved	Totals
New drug	60	40	100
Old drug	50	50	100
Totals	110	90	200

IX. CORRELATION AND REGRESSION

A. Introduction: Correlation vs. Regression

1. Correlation examines the strength and direction of the association between two variables (e.g., when one variable increases, another variable increases or decreases). Correlation does not necessarily reflect that one variable is useful in predicting the other.
2. Regression examines the ability of one or multiple variables to predict a dependent variable. In the medical literature, regression is commonly used to determine whether differences exist between groups after controlling for confounding factors. Regression can also be used to determine the level of importance (weight and strength) that an independent variable plays in predicting a dependent variable.

B. Pearson Correlation

1. A measure of the strength of the relationship between two continuous variables that are normally distributed and linearly related
2. Often called the degree of association between the two variables
3. Unlike in regression analysis, correlation coefficients do not inform the reader whether one variable is predictive of another.
4. Pearson correlation coefficient (r) ranges from -1 to $+1$ and can take any value in between:

-1 Perfect negative linear relationship	0 No linear relationship	$+1$ Perfect positive linear relationship

5. Hypothesis testing is performed to determine whether the correlation coefficient is different from zero. This test is highly influenced by sample size.

C. Pearls About Correlation

1. The closer the r is to 1 (either + or -), the more highly correlated the two variables. The closer the r is to 0, the weaker the relationship between the two variables.
2. There is no agreed-on or consistent interpretation of the value of the correlation coefficient. It depends on the environment of the investigation (laboratory vs. clinical experiment).
3. Pay more attention to the magnitude of the correlation than to the p value because the p value is influenced by sample size.
4. Interpretation of the graphic representation of the two variables is important for the proper use of correlation analysis. Visually inspecting a scatterplot of the two variables before using correlation analysis is essential (Figure 2).

D. Spearman Rank Correlation: Nonparametric test of the strength of an association between two continuous variables that does not assume a normal distribution. This test can be used for ordinal data or continuous data that are not normally distributed.

E. Regression

1. A statistical technique used to determine whether one variable, including treatment group, predicts another. There are many different types (e.g., simple linear regression tests if one continuous outcome [dependent] variable is predicted by one continuous independent (causative) variable).
2. Two main purposes of regression: (1) develop prediction model and (2) estimate the accuracy of prediction
3. Prediction model: Making predictions of the dependent variable from the independent variable; for example, a simple linear model is $Y = mx + b$ (dependent variable = slope $\times$ independent variable + intercept). If the independent variable is treatment group, the model will predict whether treatment group influences the outcome of interest.
4. Accuracy of prediction: How well the independent variable predicts the dependent variable
 - a. Regression analysis determines the extent of variability in the dependent variable that can be explained by the independent variable.
 - b. Coefficient of determination (r^2) is often reported to describe this relationship. Values of r^2 can range from 0 to 1; for example, an r^2 of 0.80 could be interpreted as saying that 80% of the variability in Y is “explained” by the variability in X .
 - c. The r^2 does not provide a mechanistic understanding of the relationship between X and Y ; rather, it provides a description of how clearly such a model (linear or otherwise) describes the relationship between the two variables.
 - d. As with the interpretation of r , the interpretation of r^2 is dependent on the scientific audience (e.g., clinical research, basic research, social science research) to which it is applied.
5. For simple linear regression, two statistical tests can be used: (1) test the hypothesis that the y -intercept differs from zero and (2) test the hypothesis that the slope of the line is different from zero.
6. Regression is useful in constructing predictive models. The process involves developing a formula for a regression line that best fits the observed data (e.g., the equations we use for predicting aminoglycoside concentrations in children or for developing the dosing algorithms for aminoglycoside dosing in the NICU [neonatal intensive care unit]).
7. Similar to correlation analysis, there are many different types of regression analysis.
 - a. Multiple linear regression: One continuous dependent variable and two or more continuous or categorical independent or explanatory variables, which allows the investigator to discern the effect of one or more variables on a dependent variable while controlling for the effects of other independent variables

- b. ANCOVA: A multiple regression model that includes both continuous and categorical independent variables. ANCOVA allows the investigator to discern the effect of one or more categorical variables (factors) on a dependent variable while controlling for the effects of one or more continuous variables (covariates).
 - c. Simple logistic regression: One categorical response variable and one continuous or categorical explanatory variable
 - d. Multiple logistic regression: One categorical dependent response variable and two or more continuous or categorical explanatory variables, which allows the investigator to discern the effect of one or more variables on a dependent variable while controlling for the effects of other covariates
 - e. Nonlinear regression: Variables are not linearly related (or cannot be transformed into a linear relationship). This is where our pharmacokinetic (PK) equations come from.
 - f. Polynomial regression: Any number of response and continuous variables with a curvilinear relationship (e.g., cubed, squared)
 - g. Common error: Health care providers often make predictions outside the range of the data collected.
8. Example of regression
- a. The following data are from a study evaluating enoxaparin use. The authors were interested in predicting patient response (measured as antifactor Xa concentrations) from the enoxaparin dose in the 75 subjects studied.

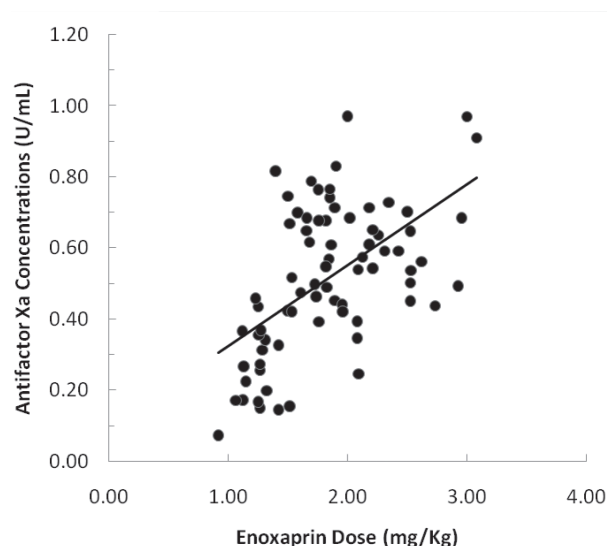


Figure 2. Relationship between antifactor Xa concentrations and enoxaparin dose.

- b. The authors performed regression analysis and reported the following: slope: 0.227, y-intercept: 0.097, $p < 0.05$, $r^2 = 0.31$

X. SURVIVAL ANALYSIS

- A. Studies the Time Between Entry in a Study and Some Event (e.g., death, myocardial infarction)
 1. The outcome variable of interest is the time until the occurrence of an event.
 2. Observations are called censored when the information concerning the survival time is incomplete. Subjects sometimes leave a study for reasons other than the event of interest (e.g., lost to follow-up) or do not experience the event before the end of the study.

3. Allows for the reality that not all subjects enter the study at the same time
4. Standard methods of statistical analysis (e.g., t-tests and linear or logistic regression models) cannot be applied to survival data because of censoring.
5. Survival methods correctly use information from both censored and uncensored observations.
6. Survival and hazard functions are key concepts in survival analysis. The survival function gives the probability of surviving or not experiencing an event up to that time for each time interval, whereas the hazard function gives the potential that the event will occur per unit of time, considering that the subject has survived up to that time.

B. Estimating the Survival Function:

1. Kaplan-Meier method

- a. Uses survival times (or censored survival times) to estimate the proportion of people who would survive a given length of time under the same circumstances
- b. Allows the production of a table ("life table") and a graph ("survival curve") (Figure 3)
- c. Readers can visually inspect the curves, but they need a test to evaluate them formally.

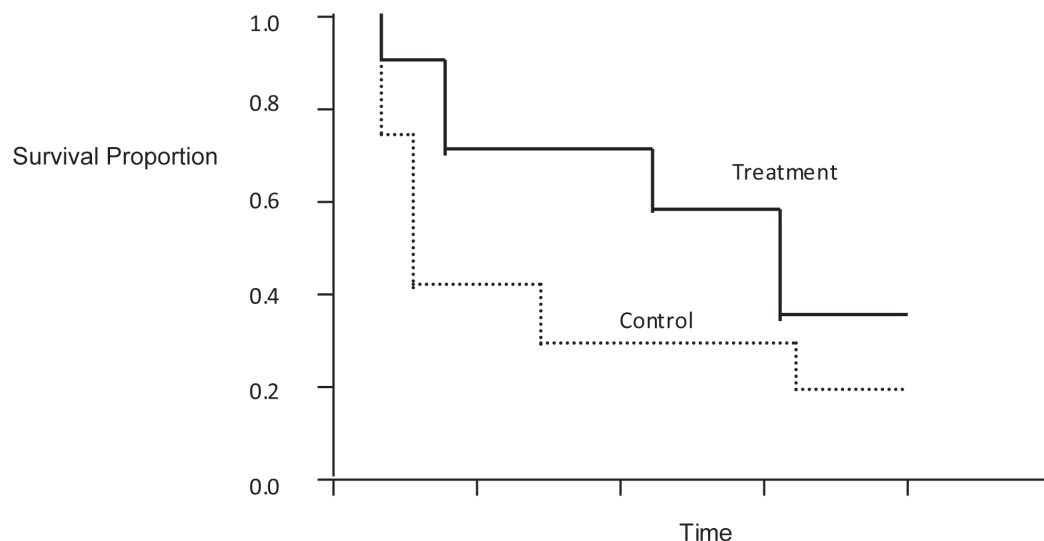


Figure 3. Survival curve.

2. Log-rank test: Compares the survival distributions between (two or more) groups
 - a. This test precludes an analysis of the effects of several variables or the magnitude of difference between groups or the CI (see below for Cox proportional hazards model).
 - b. H_0 : No difference in survival between the two populations
 - c. Log-rank test uses several assumptions:
 - i. Random sampling and subjects chosen independently
 - ii. Consistent criteria for entry or end point
 - iii. Baseline survival rate does not change as time progresses.
 - iv. Censored subjects have the same average survival time as uncensored subjects.
3. Cox proportional hazards model
 - a. Most popular method to evaluate the impact of covariates: Reported (graphically) like Kaplan-Meier (Figure 2)
 - b. Allows the investigation of the influence of several independent variables at the same time
 - c. Actual method of construction and calculation is complex

- d. Compares survival in two or more groups after adjusting for other variables
- e. Allows calculation of a hazard ratio and CIs

XI. SELECTED REPRESENTATIVE STATISTICAL TESTS

Table 5. Representative Statistical Tests

Type of Variable	2 Samples (independent)	2 Samples (related)	> 2 Samples (independent)	> 2 Samples (related)
Nominal	Chi-square (χ^2) or Fisher exact test	McNemar test	χ^2	Cochran Q
<i>1 Confounder</i>	Mantel-Haenszel or logistic regression	Rare	χ^2	Rare
≥ 2 Confounders	Logistic regression	Rare	Logistic regression	Rare
Ordinal	Wilcoxon rank sum Mann-Whitney U test	Wilcoxon signed rank Sign test	Kruskal-Wallis (MCP)	Friedman ANOVA
<i>1 Confounder</i>	2-way ANOVA ranks	2-way repeated ANOVA ranks	2-way ANOVA ranks	2-way repeated ANOVA ranks
≥ 2 Confounders	ANOVA ranks	Repeated-measures regression	ANOVA ranks	Repeated-measures regression
Continuous <i>No factors</i>	Equal variance t-test Unequal variance t-test	Paired t-test	1-way ANOVA (MCP)	Repeated-measures ANOVA
<i>1 Confounder</i>	ANCOVA or multiple linear regression	2-way repeated-measures ANOVA	2-way ANOVA	2-way repeated-measures ANOVA
≥ 2 Confounders	ANCOVA or multiple linear regression	Repeated-measures regression	ANCOVA	Repeated-measures regression

MCP = multiple comparison procedures.

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

The Spearman rank correlation is a nonparametric test of the strength of an association between two ordinal or continuous variables (Answer C is correct). Answer A is incorrect because the Pearson correlation requires the variables of interest to be continuous, and Answer D is incorrect because regression analysis is used to develop predictive models and requires continuous data. Answer B is incorrect because the ANOVA is used to test for differences between three or more groups, not correlation between two variables.

2. Answer: B

Answer B is correct and Answer C is incorrect because the CI can be used to determine whether a statistically significant difference was observed between groups and to estimate the size of the difference. Answer A is incorrect because the p value can be used to determine whether there is a statistically significant difference between groups, and Answer D is incorrect on both accounts; the p value shows statistical significance but does not give the reader an estimate of the size of the difference between groups.

3. Answer: C

The Wong-Baker FACES pain rating scale is an ordinal scale, and the Wilcoxon rank sum is a nonparametric test that can be used to compare ordinal data between two independent groups (Answer C is correct). Answers A and B are incorrect because both the Student t-test and the paired Student t-test are parametric tests and would not be appropriate for data on an ordinal scale. Answer D is incorrect because the Pearson correlation test is used to determine the strength of association between two continuous variables.

4. Answer: C

Even though both the Wilcoxon signed rank and the Wilcoxon rank sum tests can be used for ordinal data, the Wilcoxon signed rank test is for paired samples (Answer C is correct), whereas the Wilcoxon rank sum test is designed for independent groups (Answer B is incorrect). Answer A is incorrect; although the paired Student t-test can be used in a paired design, the criteria for using this parametric test include continuous, normally distributed data. The McNemar test can be used for a study that has a paired design; however, Answer D is incorrect

because the test is designed for nominal versus ordinal data, and use of this test would result in less power to find a difference.

5. Answer: B

For a continuous variable that is normally distributed, using the mean and SD is the most informative way to report the results compared with the other options listed (Answer B is correct). By reporting these two parameters, the reader will be able to re-create the distribution of the results. Although Answer A would not be an incorrect way of reporting the results, it is not the best answer because median and IQR would not be as informative and do not require that the results be normally distributed. Answer C is incorrect because the SE is not a reflection of the distribution of the sample data; rather, it is an estimate of how well the investigator estimated the mean of the population sampled. Mode represents the most frequent result. Although the mode would be expected to be equal to the mean if the data were normally distributed, it is rarely reported in the clinical literature and, if reported with the range, would not be as informative as the mean and SD; therefore, Answer D is incorrect.

6. Answer: A

The paired Student t-test is the best option because the investigators have results for each subject before and after the use of drug X (Answer A is correct). Although the Wilcoxon signed rank test is designed to compare paired samples, Answer B is incorrect because it is a nonparametric test and would have less power. Answer C is incorrect because although the ANOVA test could be used, this test assumes that groups are not paired, and it would have less power to find a difference. The chi-square test is a nonparametric test for nominal data; therefore, Answer D is incorrect.

7. Answer: B

Estimating the sample size needed to achieve a predetermined power ($\text{power} = (1 - \beta)$) or the likelihood of finding a difference depends on several factors. Increasing the delta or the difference the investigator feels a priori is the minimal clinically significant difference will decrease the sample size estimate, allowing the investigators to stay within their limited budget (Answer B is correct). Answers A, C, and D are incorrect because

choosing a smaller α (risk of error you will tolerate when rejecting H_0), an outcome measure that has increased variability compared with the LDL, or a parallel versus a paired study design will result in a decrease in power; therefore, the investigators will have to increase the sample size to maintain the same power to detect a difference between groups, which is the opposite of their goal.

8. Answer: A

Answer D is not the best answer because the 95% CI will allow readers to better estimate the clinical significance of the reported difference and how that may apply to their practice goals in addition to determining whether the difference reported is statistically significant (Answer A is correct); the p value will report only the latter. Answers B and C are incorrect because neither reports whether a difference was observed between treatment groups; Answer B estimates the change from baseline in each group separately, and Answer C is a descriptive statistic of the LDL in each group after 1 year of treatment.

9. Answer: A

The ANCOVA test is a multiple regression model that includes both continuous (covariates) and categorical (factors) independent variables, which will allow the investigators to discern the effect of drug X while controlling for the effects of one or more continuous variables (Answer A is correct). The ANCOVA test allows the investigator to determine whether a continuous dependent variable differs between groups while controlling for other continuous or categorical dependent variables; although not a choice listed, multiple linear regression would be an acceptable method as well. Answers B-D are incorrect because they are all statistical tests for determining differences between groups that do not allow the investigator to control for covariates.

10. Answer: D

Survival analysis allows investigators to study the time between study entry and an event such as death. The Cox proportional hazards model is a method of survival analysis that compares survival in two or more groups after adjusting for the effect of other variables (Answer D is correct). Answers A-C are incorrect because they are all statistical tests for determining differences between groups; unlike survival analysis, they do not allow investigators the ability to include censored and uncensored data.

11. Answer: B

An OR greater than 1 indicates an increase in the odds of having an outcome (Answer B is correct). Answers A and D are incorrect because the 95% CI does not include 1; therefore, the difference in odds is statistically significant, and a p value does not need to be reported. Answer C is incorrect because children without cancer have a lower versus higher odds of having the outcome.

12. Answer: B

	Outcome Yes	Outcome No	Total
Drug A	30 (a)	20 (b)	50
Drug B	20 (c)	30 (d)	50
Total	50	50	100

The relative risk or risk ratio is the ratio of the incidence observed in each group $((30/50)/(20/50))$ (Answer B is correct). Answer C is incorrect because it is the OR; the difference in results between Answer C and Answer B emphasizes how the OR differs from the relative risk or risk ratio when the incidence is not rare. The OR is calculated by cross-multiplying and dividing the observed number of events (ad/bc) . Answer A is incorrect because it is the calculation of the OR of drug B compared with drug A. Answer D is incorrect because of a decimal point error, making the answer 10 times too large.

13. Answer: A

One assumption of both the Student t-test and the paired Student t-test is that the data are continuous (Answer A is correct). Other assumptions include normal distribution and homogeneity of variance between groups. Answers B and D are incorrect because nominal data are a form of discrete data and discrete data are not continuous. Answer C is incorrect; although ordinal data are similar to continuous data because the data can be placed in order, the difference between any units within the scale is not the same.

14. Answer: C

Using the mean and SD is the most informative way to report the results according to the type and distribution of the data; these two variables allow the reader to re-create the distribution of the results (Answer C is correct). Answer B is incorrect because the median is commonly reported with the middle 50% of the data (IQR) versus the SD. Although the median and IQR would not

be inappropriate, Answer D is incorrect because the median and IQR are not as informative as the mean and SD, which require a normal distribution of the results. Answer A is incorrect because the SE is an estimate of how accurately the sample estimate reflects the true mean of the population sampled and does not represent the distribution of the data.

15. Answer: C

In addition to showing whether there is a statistically significant difference between groups, the 95% CI gives the reader an estimate of how accurately the study estimated the true difference in the population sampled, which can in turn help the reader discern whether a difference is clinically significant (Answer C is correct). Answer A is incorrect because the p value shows only the likelihood of a type I error. Answers B and D are incorrect because median and variance are descriptive statistics, neither of which would allow the reader to estimate the likelihood that the difference occurred by chance.

16. Answer: A

Kruskal-Wallis is a nonparametric statistical test appropriate for comparing three or more independent groups (Answer A is correct). Answers B and C are incorrect because the Student t-test and ANOVA are parametric tests that require continuous data. Although ordinal data can be analyzed with the Friedman ANOVA, Answer D is incorrect because this is a repeated-measures test, and the groups are independent.

STUDY DESIGNS: DESIGN AND APPLICATION

MATE M. SORIC, PHARM.D., FCCP, BCPS

**NORTHEAST OHIO MEDICAL UNIVERSITY COLLEGE OF PHARMACY
ROOTSTOWN, OHIO**

STUDY DESIGNS: DESIGN AND APPLICATION

MATE M. SORIC, PHARM.D., FCCP, BCPS

**NORTHEAST OHIO MEDICAL UNIVERSITY COLLEGE OF PHARMACY
ROOTSTOWN, OHIO**

Learning Objectives

1. Define, compare, and contrast the concepts of internal and external validity, bias, and confounding in clinical study design.
2. Compare and contrast the advantages and disadvantages of various study designs (e.g., prospective; retrospective; case-control; cohort; cross-sectional; randomized controlled clinical trials; systematic review; meta-analysis).
3. Delineate the difference between parallel and crossover study designs.
4. Define and evaluate odds, odds ratio, risk/incidence rate, risk ratio/relative risks (RRs), and other risk estimates.
5. Compute and evaluate number needed to treat and number needed to harm.
6. Define and calculate terms such as absolute risk difference and RR difference.
7. Define and calculate terms such as true positive, false positive, true negative, false negative, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio.
8. Define research, quality improvement, institutional review boards, and the peer review process.

Self-Assessment Questions

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

Questions 1 and 2 pertain to the following case.

A recently released immune globulin product is associated with fewer infusion-related reactions than other currently available immune globulins. After 2 years of use, the manufacturer did a retrospective case-control study after 20 different reports of severe infusion reactions were sent to the FDA's MedWatch program. Other risk factors for infusion reactions were similar between the groups. Interviewers were thoroughly trained, and a data monitoring committee validated the data collection process.

1. Which type of bias is this study design most susceptible to?
 - A. Selection.
 - B. Recall.

C. Interviewer.

D. Misclassification.

2. Which factor will be most affected by the type of bias likely to occur in this study?
 - A. External validity.
 - B. Internal validity.
 - C. Randomization.
 - D. Study recruitment.
3. When describing the results of a randomized controlled clinical trial, an investigator reports using an intention-to-treat analysis to analyze the data. The results of the investigation comparing two diuretics for heart failure show no difference in the number of hospitalizations for decompensated heart failure between the treatment groups. Given the method of data analysis, which statement is most appropriate regarding the trial?
 - A. May be susceptible to issues regarding recall bias.
 - B. Provides a good measure of effectiveness under typical clinical conditions.
 - C. Cannot provide an estimate of the intervention's effectiveness.
 - D. May overestimate the actual treatment effect.

Questions 4 and 5 pertain to the following case.

A new prospective randomized study compared once-daily mometasone with twice-daily mometasone in a pediatric population with asthma. One of the study end points was hospitalizations for asthma exacerbations. The following table summarizes hospitalization rates in all patients.

	Once-Daily Mometasone	Twice-Daily Mometasone
Rate of asthma-related hospitalization, n (%)	13 of 298 (4.4)	9 of 312 (2.9)

The 95% confidence interval (CI) for the difference in hospitalization rates between the two groups was -1.5% to 4.5%.

4. Which conclusion is most appropriate?
 - A. Twice-daily mometasone is superior to once daily.
 - B. The superiority of twice-daily mometasone could not be established over once daily.
 - C. Once-daily mometasone is noninferior to twice daily.
 - D. No conclusion can be made because p values are unavailable.
5. According to the data in the previous question and the result obtained, which best represents the number of patients needed to treat (NNT) with twice-daily mometasone to prevent one asthma-related hospitalization?
 - A. 2.
 - B. 67.
 - C. 152.
 - D. Cannot be calculated because the result was nonsignificant.
7. When the study was being designed, which best describes the outcome for which the study was most likely to have been powered?
 - A. Differences in the rate of the composite outcome, seizure events.
 - B. Differences in the rate of seizure-related ED visits.
 - C. Differences in the rate of the composite outcome in female patients.
 - D. Differences in the rate of the composite outcomes in male patients.
8. In a novel meta-analysis of observational studies examining the effects of several chemotherapy regimens on Hodgkin lymphoma, the odds ratio (OR) for treatment with ABVD (doxorubicin, bleomycin, vincristine, dacarbazine) compared with ABVE (doxorubicin, bleomycin, vincristine, etoposide) for 5-year cancer recurrence was 0.84 (95% CI, 0.75–0.95). Which statement most appropriately interprets these findings?
 - A. Treatment of Hodgkin lymphoma with ABVD was more effective in preventing cancer recurrence than treatment with ABVE.
 - B. Treatment of Hodgkin lymphoma with ABVE was more effective in preventing cancer recurrence than treatment with ABVD.
 - C. Difference between treatment with ABVE and treatment with ABVD is not statistically significant.
 - D. Odds of cancer recurrence when treating Hodgkin lymphoma with ABVD are lower than when treating with ABVE.

Questions 6 and 7 pertain to the following case.

A newly published multicenter, double-blind, placebo-controlled trial randomly assigned 4837 pediatric patients with epilepsy to treatment with a ketogenic diet or a standard pediatric diet. The primary combined end point was the rate of seizure events, defined as the composite of seizure-related emergency department (ED) visits, hospitalizations, or emergency administration of benzodiazepine therapy. Data were analyzed according to intention-to-treat analysis using a Cox proportional hazards model. The hazard ratio (HR) and 95% CI for the ketogenic diet group were 0.91 and 0.78–1.05, respectively. In the prespecified subgroup of female patients, the ketogenic diet was associated with an HR of 0.73 (95% CI, 0.51–1.03).

6. Which statement is most appropriate?
 - A. The ketogenic diet statistically significantly reduced the risk of seizures ($p < 0.05$).
 - B. The ketogenic diet statistically significantly reduced the risk of seizures ($p < 0.01$).
 - C. The ketogenic diet did not significantly reduce the risk of seizures ($p > 0.05$).
 - D. Without a p value, it is impossible to determine whether the ketogenic diet affected seizure events.
9. According to the Code of Federal Regulations, which statement best describes what is required of institutional review board (IRB) membership?
 - A. At least one layperson must serve on the IRB.
 - B. Size of IRB membership changes depending on institution size.
 - C. At least 10 members must serve on the IRB.
 - D. There must be one physician on the IRB.

10. As a clinician who recently completed a research project, you are writing the introduction section of the paper. Which piece of information would best be included in the introduction section of a paper for a completed research project?
- A. Information related to the process of selecting participants.
 - B. Summary of prior studies.
 - C. Average age of the study subjects.
 - D. Acknowledgments of the clerical staff.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 3: Information Management, Research, and Education; Task(s): 3.3, 3.4, 3.5

I. INTRODUCTION

- A. Why Do Pediatric Pharmacists Need to Know About Study Design and Interpretation?
 - 1. *Pediatric Pharmacy Specialty Examination content outline*, Domain 3: Information Management, Research, and Education (17%)
 - 2. Task statements:
 - a. Task 3.3: Contribute to the pediatric body of knowledge (e.g., conduct or participate in research, deliver presentations, participate as peer reviewer, publish).
 - b. Task 3.4: Retrieve and interpret biomedical literature with regard to study methodology, statistical analysis, study results, and applicability to pediatric pharmacy practice.
 - c. Task 3.5: Develop and maintain a pediatric-specific medical reference library.
 - 3. Knowledge of:
 - a. k3.4 Research design, methodology, statistical analysis, and clinical application of published data
 - b. k3.5 Regulatory, IRB, human subjects safety requirements and concerns for conducting research in the pediatric population (e.g., consent, assent, investigational drugs, risk)
 - c. k3.6 Dissemination of pediatric information and scholarly activity (e.g., presentations, manuscripts, newsletters, abstracts, posters)
 - d. k3.7 Pediatric-specific references

II. VARIOUS ISSUES IN STUDY DESIGN

- A. Research Design Classification
 - 1. Study purpose: Descriptive (summarizes information such as who, what, when, and where) versus analytic (understanding relationships or cause and effect)
 - 2. Time orientation: Prospective versus retrospective design
 - a. Prospective: Begin in the present and progress forward, collecting data from subjects whose outcomes lie in the future.
 - b. Retrospective: Typically begin and end in the present; however, this design involves a backward look to collect information about events that occurred in the past.
 - 3. Investigator orientation: Interventional versus quasi-experimental. Researcher intervenes in interventional study designs. The strongest interventional study is a randomized controlled trial (RCT). Quasi-experimental is a study design that lacks true randomization and instead uses some other method to assign groups (e.g., pre-post study).
 - 4. Experimental setting
 - a. RCTs (Figure 1)
 - b. Observational trials

B. Relative Strength of Evidence: Hierarchy of Study Designs

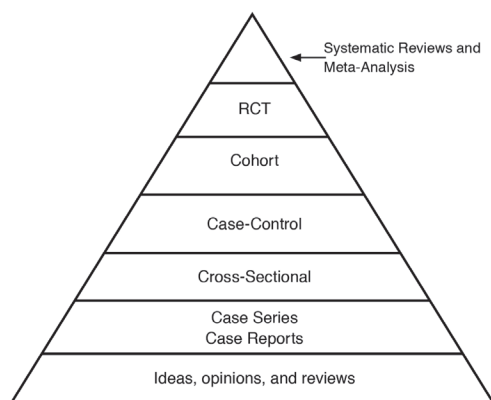


Figure 1. Hierarchy of clinical study design.

RCT = randomized controlled trial.

C. Validity in Study Design

1. Internal validity

- a. Validity within the confines of the study methods
- b. Does the study design adequately and appropriately test/measure what it purports?
- c. Does the study adequately and appropriately address bias, confounding, and measurement of end points?

2. External validity

- a. Validity related to generalizing the study results outside the study setting
- b. Can the results be applied to other groups, patients, or systems?
- c. Addresses issues of generalizability and representativeness

D. Bias in Study Design

1. Definition: Systematic, nonrandom variation in study methodology or conductance, ultimately introducing error in outcome interpretation. Bias can occur in all aspects of the study design.
2. Examples of bias (not an all-inclusive list)
 - a. Selection bias: An error in the selection of or sampling of individuals for a clinical study. Classic example: subjects chosen for the case and control groups differ in one or more characteristics that alter the outcome of a study
 - b. Observational, information, or misclassification bias: An error in the recording of individual factors of a study, such as inaccurate recording of a patient's risk factor, inaccurate recording of the timing of a blood sample
 - i. Differential: Proportion of misclassification is different between the two study groups.
 - ii. Non-differential: Proportion of misclassification is the same between the two groups.
 - c. Recall (or reporting) bias: An error in which the two study groups differ in their recollection of past exposures or other events. Classic example: Studies of birth defects secondary to medications exposure during pregnancy
 - d. Interviewer bias: Classic example: Interviews are not conducted in a uniform manner for all study participants.
3. Controlling for bias
 - a. Design: Choosing proper inclusion and exclusion criteria, implementing proper sampling methods
 - b. Means of collecting data
 - c. Sources of information (regarding disease and exposure)
 - d. Analysis: Often difficult to control for bias during data analysis once bias is introduced to the study

E. Confounding in Study Design

1. A variable that affects the independent or dependent variable, altering the ability to determine the true effect on the measured outcome. These factors may hide or exaggerate a true association. Example: Not accounting for smoking status in a trial evaluating the cardiovascular effects of a new medication
2. To minimize the potential for missing a confounding variable, all relevant information should be collected and evaluated.
3. Controlling for confounding
 - a. During the design of a study
 - i. Randomization
 - ii. Restriction: Restrict entry into the study to a group of subjects who have the same confounding factors.
 - iii. Matching: Ensure that the study groups do not differ with respect to possible confounders such as age and sex by matching the two comparison groups.
 - b. Analysis
 - i. Stratification: Examine the primary association of interest at different levels of a potential confounding factor.
 - ii. Multivariate analysis: Regression analysis designed to account for confounding variables
 - iii. Sensitivity analysis: Performing additional analyses to identify changes in results if certain confounders are handled differently

III. CASE REPORTS/CASE SERIES

- A. Document and describe experiences, novel treatments, and unusual events. Allows hypothesis generation that can be tested with other study designs. Note that the title does not state “study.”
 1. Possible adverse drug reactions in one or more patients: QT-interval prolongation associated with fluoroquinolone antibiotics
 2. Case report: One patient
 3. Case series: More than one patient with a similar experience or many case reports combined into a descriptive review
 4. Reports should provide sufficient detail to allow readers to recognize same/similar cases at their center/practice.
- B. Advantages and Disadvantages
 1. Advantages:
 - a. Hypotheses are formed and may be the first step in describing an important clinical problem.
 - b. Easy to perform
 - c. Inexpensive
 2. Disadvantages:
 - a. Do not provide explanation other than conjecture
 - b. Do not establish causality or association

IV. OBSERVATIONAL STUDY DESIGNS

- A. Design does not involve intervention, only observation. It is essential to remember that in most cases, observational study designs investigate associations – not causes.

B. Case-Control Study: Study exposure in those with and without the outcome of interest (Figure 2)

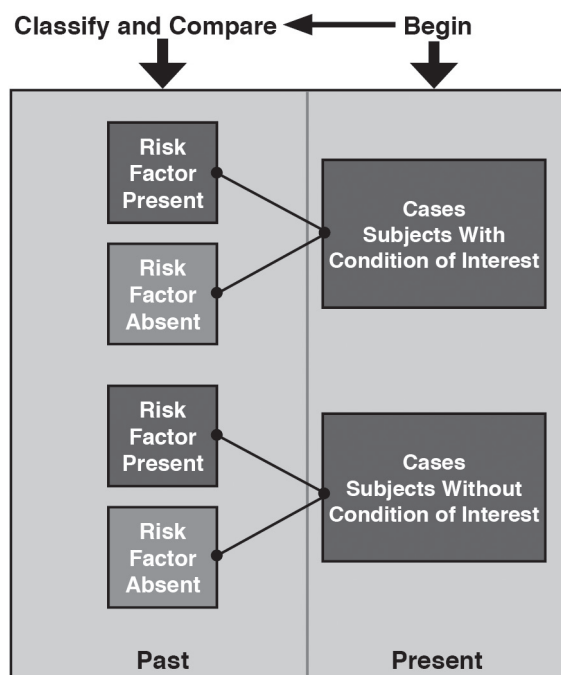


Figure 2. Case-control study design.

1. Determine the association between exposures/risk factors and disease/condition. Classic example: Aspirin use and Reye syndrome
2. Retrospective studies
3. Useful method (and perhaps the only practical way) to study exposures in rare diseases or diseases that take long periods to develop
4. Critical assumptions to minimize bias
 - a. Cases are selected to be representative of those who have the disease.
 - b. Controls are representative of the general population without the disease and are as identical as possible to the cases, minus the presence of the disease.
 - c. Information is collected from cases and controls in the same way.
5. Examples
 - a. Risk of myocardial infarction associated with antihypertensive drug therapies (JAMA 1995;274:620-5)
 - b. Phenylpropanolamine (PPA) and the risk of hemorrhagic stroke (N Engl J Med 2000;343:1826-32). Purpose of study:
 - i. To estimate the association between hemorrhagic stroke and the use of appetite suppressants containing PPA in women
 - ii. To estimate the association between any use of PPA (in appetite suppressant or cough or cold remedy) and hemorrhagic stroke
 - iii. To estimate the association between hemorrhagic stroke and the type of exposure to PPA in men and women
 - iv. Disease: Hemorrhagic stroke (several types). Exposure: PPA
 - v. Cases: Symptomatic subarachnoid or intracerebral hemorrhage (n=702). Controls: Matched subjects by sex, race, and age (n=1376)
 - vi. Exposure assessed by structured questionnaire, product photographs, and ingredient confirmation

6. Advantages
 - a. Inexpensive and can be conducted quickly
 - b. Allows investigation of several possible exposures or associations
7. Disadvantages
 - a. Confounding must be controlled.
 - b. Observational and recall bias: Looking back to recall exposures and their possible levels of exposure
 - c. Selection bias: Case selection and control matching are difficult.
8. Measure of association: OR (odds ratio): In some cases, this can be an estimate of the relative risk/ratio (RR). The OR is interpreted as the odds of exposure to a factor in those with a condition or disease compared with those who do not have the condition or disease. Interpretation of these concepts will be presented later.

C. Cohort Study

1. Determines the association between exposures/factors and disease/condition development. Allows an estimation of the risk of outcome (and the RR between the exposure groups). Studies outcome of interest in those with and without the exposure of interest. Classic examples follow:
 - a. Framingham Study. A “cohort” of subjects from Framingham, Massachusetts, were (and are) studied over time to evaluate the relationship between a variety of conditions (exposures) on the development of cardiovascular disease.
 - b. Nurses’ Health Study: Investigated the potential long-term consequences of the use of oral contraceptives
2. Describes the incidence or natural history of a disease/condition and measures it in time sequence; can be retrospective or prospective
3. Retrospective (historical) (Figure 3): Outcomes identified in the present but involves a backward look to collect information about events/risk factors that occurred in the past
 - a. Example: Vaccine 2022;40:1790-8

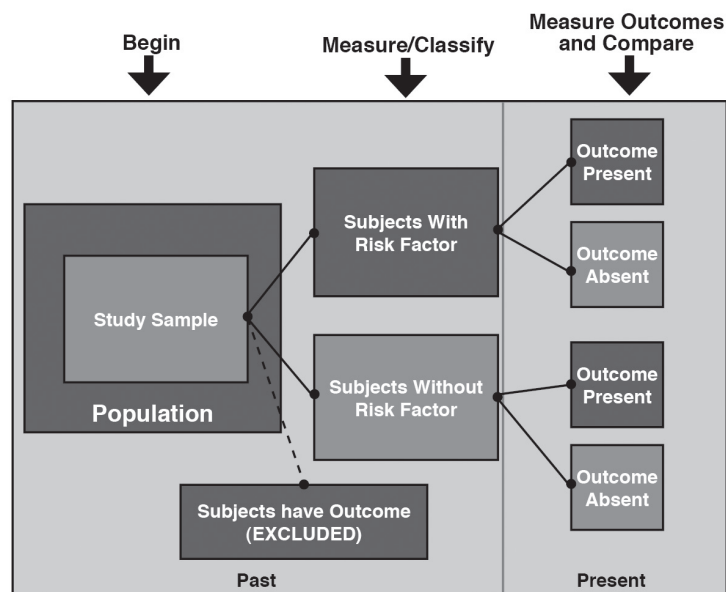


Figure 3. “Retrospective” (historical) cohort study design.

- b. Advantages: Less expensive and less time-consuming; no loss to follow-up; ability to investigate issues not amenable to a clinical trial or ethical or safety issues
- c. Disadvantages: Only as good as the data available; little control of confounding variables through nonstatistical approaches; recall bias

4. Prospective (longitudinal) (Figure 4): Begin in the present and progress forward, collecting data from subjects whose outcomes lie in the future.

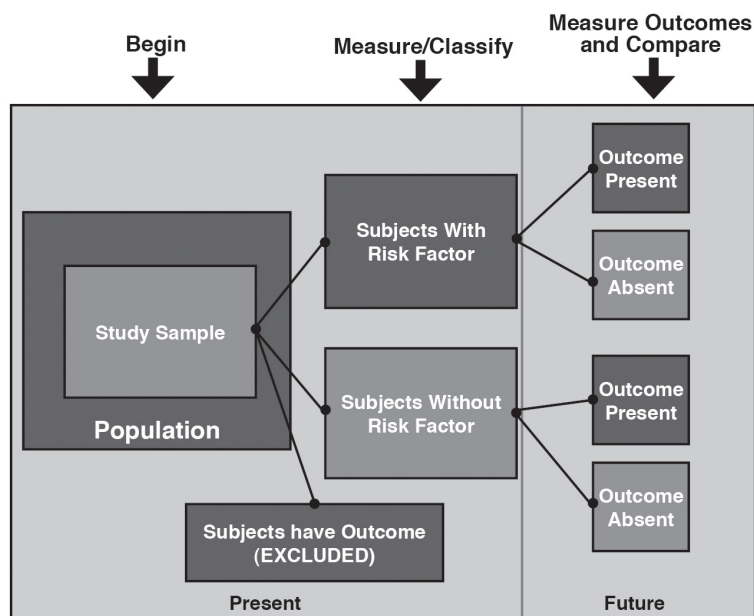


Figure 4. Prospective cohort study design.

- a. Example: Prospective, observational study: Postmenopausal hormone use and secondary prevention of coronary events in the Nurses' Health Study (Ann Intern Med 2001;135:1-8)
 - b. Advantages: Can control for confounding factors to a greater extent; easier to plan for data collection
 - c. Disadvantages: More expensive and time-intensive; loss of subject follow-up; difficult to study rare diseases/conditions at a reasonable cost
 5. Measure of association: RR: The risk of an event or development of a condition relative to exposure; the risk of someone developing a condition when exposed compared with someone who has not been exposed
- D. Cross-sectional (a.k.a. prevalence study)
1. Identify the prevalence or characteristics of a condition in a group of individuals at a particular point in time or time interval.
 2. Examples
 - a. Population-based, cross-sectional study: Prevalence of serious eye disease and visual impairment in a north London population (BMJ 1998;316:1643-7)
 - b. Cross-sectional analysis of data from a large cohort study: Maternal characteristics and migraine pharmacotherapy during pregnancy (Cephalgia 2009;29:1267-76)
 3. Advantages: Easy design; "snapshot in time," all data collected at one time; studies are accomplished by questionnaire, interview, or other available biomedical information (e.g., laboratory values)
 4. Disadvantages: Does not allow the study of a factor (or factors) in individual subjects over time, just at the time of assessment; difficult-to-study rare conditions

V. INCIDENCE, PREVALENCE, RELATIVE RISK/RISK RATIOS, AND ODDS RATIOS

A. Incidence

1. Measure of the probability of developing a disease
2. Incidence rate: Number of new cases of disease per population in a specified time
3. Calculated by dividing the number of individuals who develop a disease during a given period by the number of individuals who were at risk of developing a disease during the same period

B. Prevalence

1. Measure of the number of individuals who have a condition/disease at any given time
2. Point prevalence: Prevalence at a particular time
3. Period prevalence: Prevalence in a period (e.g., year, month)

C. Interpreting Relative Risk/Risk Ratios (RRs) and Odds Ratios (ORs)

1. Estimate the magnitude of association between exposure and disease. Key point: For observational studies, this is not cause and effect; it is a measure of association.
2. The RR cannot be directly calculated for most case-control studies; instead, the OR is usually an estimate of the RR.
3. The RR and OR are interpreted on the basis of their difference from unity (1.0). If the 95% confidence interval (CI) includes unity, no statistical difference is indicated. The CI also gives us an idea of the spread within which the true effect lies. Though unity is 1.0 for RR and OR, when looking at absolute rather than relative end points, unity is 0.0.
4. Interpretation of the index of risk
 - a. Direction of risk (Table 1)

Table 1. Direction of Risk Associated with OR and RR

RR or OR	Interpretation
< 1	Negative association RR: Risk of disease is lower in the exposed group OR: Odds of exposure is lower in the diseased group
= 1	No association RR: Risk of disease in the two groups is not significantly different OR: Odds of exposure in the two groups is not significantly different
> 1	Positive association RR: Risk of disease is greater in the exposed group OR: Odds of exposure is greater in the diseased group

OR = odds ratio; RR = relative risk/risk ratio.

b. Magnitude of risk (Table 2)

Table 2. Magnitude of Risk Associated with OR and RR

RR or OR	Interpretation
0.75	25% reduction in the risk/odds
1.0	No difference in risk/odds
1.5	50% increase in the risk/odds
3.0	3-fold (or 200%) increase in the risk/odds

OR = odds ratio; RR = relative risk/risk ratio.

5. Calculating RR/OR/contingency tables (Tables 3 and 4)

Table 3. Contingency Table for Estimating RR and OR

		Disease?	
		Yes	No
Exposure?	Yes	A	B
	No	C	D

- RR total incidence of disease in exposed/total incidence of disease in unexposed
 - $RR = [A/(A + B)]/[C/(C + D)]$
 - OR odds of exposure in cases/odds of exposure in controls
 - $OR = (A/C)/(B/D)$ or $(A \times D)/(B \times C)$
6. Example: (PPA study)

Table 4. Contingency Table

		Disease? Hemorrhagic Stroke in Women	
		Yes	No
Exposure? Appetite suppression use	Yes	6	1
	No	377	749

From: Kernan WN, Viscoli CM, Brass LM, et al. Phenylpropanolamine (PPA) and the risk of hemorrhagic stroke. N Engl J Med 2000;343:1826-32.

- $OR = (6/377)/(1/749) = 12$
- Data from the PPA study above related to appetite suppressant and development of hemorrhagic stroke in women (Table 5)

Table 5. Use of PPA and Appetite Suppressants and the Risk of Developing Hemorrhagic Stroke

	Cases (+ hemorrhagic stroke) n=383	Controls (- hemorrhagic stroke) n=750	Adjusted OR (95% CI)
Appetite suppressant: Women	6	1	16.6 (1.51–182)
Appetite suppressant: Men	0	0	—
Appetite suppressant: Either	6	1	15.9 (1.38–184)
PPA: Women	21	20	1.98 (1.00–3.90)
PPA: Men	6	13	0.62 (0.20–1.92)
PPA: Either	27	33	1.49 (0.84–2.64)

CI = confidence interval; OR = odds ratio; PPA = phenylpropanolamine.

- c. What do these numbers mean?
 - d. Can you interpret the OR and 95% CI in all cases?
 - i. What does the point estimate (OR) mean?
 - ii. What does the CI mean?
 - iii. Which ones are statistically significant?
- D. Causation
1. REMEMBER: In general, we do not prove or show causality with observational studies, but there is some general “guidance” to consider when evaluating them. It is important to recognize that, in many situations, the conduct of studies to establish causality is not possible, practical, or ethical.
 2. Questions used to evaluate causality
 - a. Was statistical significance observed?
 - b. What was the strength of the association, as measured by the OR or the RR?
 - c. Were dose-response relationships evaluated?
 - d. Was there a temporal relationship between exposure and disease/outcome?
 - e. Have the results been consistently shown?
 - f. Is there another identifiable cause for the outcome?
 - g. Is there biologic plausibility to the causation?
 - h. Are the results consistent with preclinical expectations and previous (e.g., animal, in vitro) evidence?

VI. RANDOMIZED CONTROLLED TRIAL DESIGN

- A. Characteristics
1. Experimental or interventional: investigator makes intervention and evaluates cause and effect. Examine etiology and efficacy using comparative groups.
 2. Some previous background information or studies should exist to suggest that the intervention used will likely be beneficial.
 3. Design allows assessment of causality.
 4. Minimizes bias through randomization and/or stratification
 - a. Randomization – Decreases confounding by ensuring confounding variables are equally dispersed between the groups. Decreases bias by giving each patient an equal chance of being in either treatment group

- b. Block randomization: Experimenter divides subjects into subgroups called “blocks,” such that the variability within blocks is less than the variability between blocks. Then, subjects within each block are randomly assigned to treatment conditions.
 - c. Stratification – Ensures balance between groups for a known confounding variable
 - d. Cluster randomization: Clusters of subjects are allocated to the intervention arms using a randomly generated allocation sequence, rather than allocating each individual patient to intervention arms in turn.
5. Treatment controls
 - a. Placebo control
 - b. Active control
 - c. Historical control
6. Blinding methods
 - a. Single-blind: Either subjects or investigators are unaware of subject assignment to active/control.
 - b. Double-blind: Both subjects and investigators are unaware of subject assignment to active/control.
 - c. Triple-blind: Both subjects and investigators are unaware of subject assignment to active/control; in addition, an analysis group is unaware.
 - d. Double-dummy: Two placebos necessary to blind active and control therapies when two treatments cannot be made identical
 - e. Open-label: Everyone is aware of subject’s assignment to active/control.
7. May use parallel or crossover design (see additional information below)
 - a. Crossover provides practical and statistical efficiency.
 - b. Crossover is not appropriate for certain types of treatment questions (e.g., effect of treatment on a disease that worsens quickly over time or worsens during the study period).
8. Factorial design: A design that examines the effects of multiple factors and considers all possible combinations of the factors in a single group of subjects. Provides more information at a similar or lower cost
9. Examples
 - a. Clinical trial: Comparison of two drugs, comparison of two behavioral modifications, etc.
 - b. Educational intervention: Online course versus lecture class format
 - c. Health care intervention: Pharmacist-based health care team versus non-pharmacist-based health care team

B. Randomized Controlled Trial: Parallel Design (Figure 5)

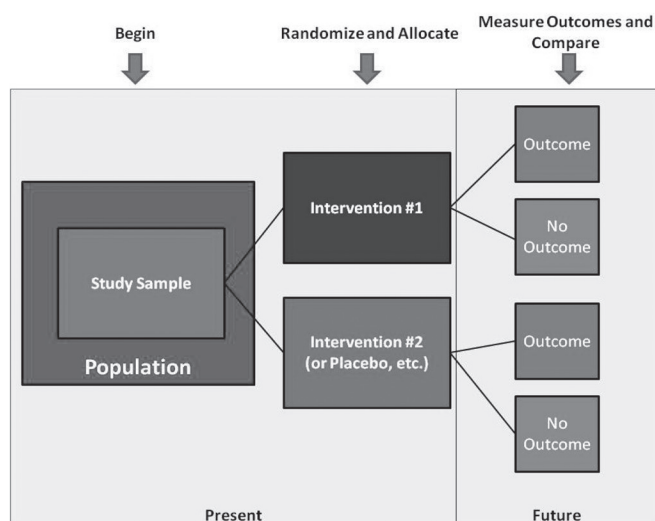


Figure 5. Randomized controlled trial: parallel design.

C. Randomized Controlled Trial: Crossover Design

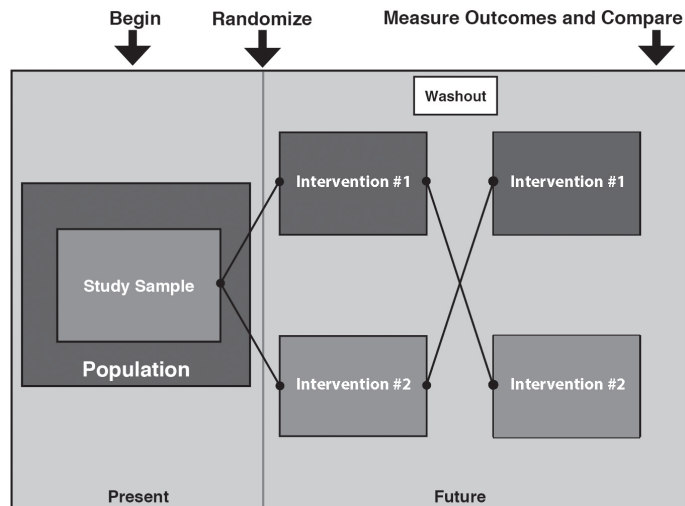


Figure 6. Randomized controlled trial: crossover design.

D. Examples of Considerations for RCTs

1. Are the results of the study valid?
 - a. Did the subjects undergo randomization before intervention, and what was the randomization technique? Did the randomization process result in equal baseline characteristics?
 - b. Were all subjects who entered the trial accounted for? Was follow-up complete? If not, how many were lost to follow-up, from which groups did they leave, and why?
 - c. Were subjects analyzed in the groups to which they were randomized? Was intention-to-treat, per-protocol, or actual treatment analysis used?
 - d. How was blinding conducted (e.g., subject, investigator), if applicable?
 - e. Were the inclusion and exclusion criteria appropriate, or were they too restrictive or inclusive? Were the groups similar at the start and end of the trial?
 - f. Was the sample size sufficient, and was a power calculation included?
 - g. Were the groups handled the same way, aside from the intervention(s)?
 - h. Were the statistical tests appropriate and understandable?
 - i. What was assessed: surrogate markers or true outcomes? Were a priori subgroup analyses performed?
2. What were the results?
 - a. How large was the treatment effect?
 - b. How precise was the effect (based on CIs)?
 - c. Did the authors properly interpret the results?
3. Can I apply the results of this study to my patient population? Will they help me care for my patients?
 - a. Can the results of this study be applied to general practice?
 - b. Was a representative population studied? Can I apply this to my setting?
 - c. Do the patients I care for fulfill the enrollment criteria for this study?
 - d. Do the patients I care for fulfill the subgroup criteria evaluated?
 - e. Do the expected benefits outweigh the expected and/or unanticipated risks?

VII. OTHER ISSUES TO CONSIDER IN RANDOMIZED CONTROLLED TRIALS

A. Subgroup Analysis

1. Important part of randomized controlled clinical trials (if set a priori). If identified post hoc, these analyses have limited utility.
2. Many times, they are overused and overinterpreted, leading to unnecessary research, misinterpretation of results, and/or suboptimal patient care.
3. Many potential pitfalls in identifying and interpreting
 - a. Failure to consider several comparisons or to adjust p values
 - b. Problems with sample size (power), classification, and lack of assessment of interaction

B. Composite End Points: Often, the impression is that this practice is not a good practice.

1. The primary end point is one of the most important decisions to make in the design of a clinical study.
2. A composite end point combines several end points.
 - a. For example, cardiovascular death, nonfatal MI, and cardiac arrest with resuscitation
 - b. Usually combines measures of morbidity and mortality
 - c. What does the following statement mean? Our findings show that ramipril reduces the rates of death, MI, stroke, revascularization, cardiac arrest, heart failure, complications related to diabetes, and new cases of diabetes in a broad spectrum of high-risk patients. Treating 1000 patients with ramipril for 4 years prevents about 150 events in around 70 patients (Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342:145-53).
 - i. Was there a reduction in all the end points or just in some?
 - ii. Are all the outcomes just as likely to occur?
 - iii. Why would the investigators of this trial have been interested in all of these outcomes?
3. What are the positives for using composite end points?
 - a. No single primary outcome
 - b. To alleviate problems of multiple testing
 - c. To increase number of events, which decreases sample size and cost to the investigator
4. What are the problems?
 - a. Difficulties in interpreting composite end points; consider our earlier example
 - b. Misattribution of statistically beneficial effects of composite measure to each of its component end points
 - c. Dilution of effects: negative results for relatively common component of composite end point “hide” real differences in other end points. Undue influence exerted on composite end point by “softer” component end points
 - d. “Averaging” of overall effect: Problems when component end points move in opposite directions; a sign the composite end point should be abandoned without valid conclusions being drawn
 - e. Should all end points be weighed the same, or should a particular end point “weigh” more?
5. The results for each individual end point should be reported together with the results for the composite.

C. Surrogate End Points

1. Parameters thought to be associated with clinical outcomes
 - a. Blood pressure and stroke prevention
 - b. Low-density lipoprotein cholesterol (LDL) reduction and cardiovascular death reduction
 - c. Premature ventricular contraction suppression and reduced mortality
2. Surrogate outcomes do not always predict clinical outcomes.
3. Short-duration studies that evaluate surrogate end points may not be large enough to detect uncommon adverse events.

D. Superiority vs. Noninferiority vs. Equivalence

1. A superiority trial is designed to detect a difference between experimental treatments. This is the typical design in a placebo-controlled clinical trial.
2. A noninferiority trial is designed to investigate whether a treatment is not clinically worse (less effective than stated margin, or inferior) than an existing treatment.
 - a. It may be the most effective, or it may have a similar effect.
 - b. Useful when placebo administration is not possible for ethical reasons
 - c. ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) (NEJM 2008; 358:1547-59)
 - i. Designed to evaluate telmisartan, ramipril, or their combination in patients with a high risk of vascular disease
 - ii. Objective was to determine whether telmisartan was noninferior to ramipril in the incidence of cardiovascular deaths.
 - iii. Noninferior difference was defined as 13% or less (the value known as delta).
 - d. Essentials of noninferiority design
 - i. Control group must be effective.
 - ii. Current study similar to previous study with control and with equal doses, clinical conditions, and design used
 - iii. Adequate power is essential, and usually, larger sample sizes are required.
3. An equivalence trial is designed to confirm the absence of a meaningful difference(s) between treatments, neither better nor worse (both directions). The key is the definition of the specified margin. What difference is important? Example: Clin Neuropharmacol 2017;40:239-42

VIII. RANDOMIZED CONTROLLED CLINICAL TRIALS: ANALYSIS**A. Randomized Controlled Clinical Trial: Application (JAMA 1998;280:605-13)**

1. RCT of estrogen plus progestin for secondary prevention of coronary heart disease (CHD) in postmenopausal women
2. Objective: To determine whether estrogen plus progestin therapy alters the risk of CHD in postmenopausal women with established CHD
3. Randomized, blinded, placebo-controlled
 - a. Two treatment arms: ERT-P (conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day) and placebo n=2763 with coronary artery disease, younger than 80 years; mean age 66.7 years
 - b. Follow-up averaged 4.1 years; 82% of patients undergoing hormone replacement therapy still taking hormone at the end of 1 year; 75% of patients still undergoing hormone replacement therapy at the end of 3 years
4. End points (Table 6)
 - a. Primary: Nonfatal MI or CHD death
 - b. Secondary: Many, including all-cause mortality. Are these composite outcomes appropriate?
5. Statistical analysis
 - a. Baseline characteristics: t-test and χ^2
 - b. Power analysis and sample size calculation
 - c. Kaplan-Meier with Cox proportional hazards model
6. Surrogate end point: LDL lowered

7. Results:

Table 6. Death and Secondary End Points by Treatment Group (Overall)

	ERT-P (%)	Placebo (%)	HR (95% CI)
Primary CHD events	12.5	12.7	0.99 (0.80–1.22)
CHD death	5.1	4.2	1.24 (0.81–1.75)
Any thromboembolic event	2.5	0.9	2.89 (1.50–5.58)
Gallbladder disease	6.1	4.5	1.38 (1.00–1.92)

CHD = coronary heart disease; CI = confidence interval; ERT-P = conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day; HR = hazard ratio.

8. Significant time trend: More CHD events in the treatment group than in placebo in year 1 and fewer in years 4 and 5
9. Author's conclusions
 - a. During follow-up, ERT-P did not reduce overall rate of CHD events.
 - b. Treatment increased rate of thromboembolic events and gallbladder disease.

B. Questions to Consider in Evaluating and Interpreting a Clinical Trial

1. Study design
 - a. Was the studied sample representative of the population or the individual to whom the results were being applied?
 - b. Were the inclusion/exclusion criteria appropriate, or were they overly restrictive or inclusive?
 - c. Sufficient sample size, power, and so forth? Was a power analysis included?
 - d. Was a study objective and/or hypothesis provided?
 - e. Was the study blinded and to whom? (subject, investigator, study personnel, or all?)
 - f. Who sponsored the trial and to what degree were they involved?
 - g. Was it a single-center or multicenter trial?
 - h. Was a run-in phase or "washout" period used? If so, why? Did it affect the interpretation of the trial?
 - i. What type of randomization method was performed? Did the randomization process produce equal baseline characteristics between all groups?
2. Outcomes/assessments
 - a. Were the primary and/or secondary outcomes identified, were they reasonable/similar to previous studies, and did they apply to clinical practice?
 - b. Was a composite outcome used, and were all the individual components identified and clearly stated in the methods and results?
 - c. Were surrogate markers used instead of (or in addition to) clinically relevant outcomes?
3. Analysis
 - a. Were baseline characteristics similar between groups?
 - b. What analysis technique was used: Intention-to-treat, actual treatment, or per-protocol?
 - c. Were the statistical tests appropriate?
4. Interpretation: Was the author's interpretation appropriate and within the confines of the study design?
5. Extrapolation
 - a. Are you applying the results to similar patients in a similar setting?
 - b. Are there possible additional adverse effects that were not measured in this study?

IX. COMMON APPROACHES TO ANALYZING CLINICAL TRIALS**A. Intention-to-Treat Analysis**

1. Compares outcomes on the basis of initial group assignment or “as randomized.” The allocation to groups was how they were “intended to be treated,” even though they may not have taken the medication for the duration of the study, dropped out, and did not comply with the protocol.
2. Determines effect of treatment under usual conditions of use. Analogous to routine clinical practice in which a patient receives a prescription but may not adhere to the prescribed drug regimen.
3. Gives a conservative estimate of differences in treatments; may underestimate treatment benefits
4. Most common approach to assessing clinical trial results
5. This is the preferred type of analysis in a superiority trial.

B. Per-Protocol Analysis

1. Subjects who do not adhere to allocated treatment are not included in the final analysis; only those who completed the trial and adhered to the protocol (based on some predetermined definition [e.g., 80% adherence]) are included.
2. Provides a lower level of evidence about treatment efficacy and more generous estimates of differences between treatments
3. Subject to several issues because of factors such as lower sample size and definitions of adherence. Results are more difficult to interpret and would be validly applied only to adherent patients like those in the trial; not necessarily generalizable to all patients

C. As-Treated Analysis

1. Subjects are analyzed by the actual intervention received. If subjects were in the active treatment group but did not take active treatment, the data would be analyzed as if they were in the placebo group.
2. This analysis essentially ignores/destroys the randomization process for those who did not adhere to the study design. Results should be interpreted with caution.

X. SYSTEMATIC REVIEW/META-ANALYSIS**A. Introduction**

1. Dramatic increase in the number of these types of papers
2. First meta-analysis probably published in 1904: Assessment of typhoid vaccine effectiveness (BMJ 1904;3:1243-6)

B. Systematic Review

1. Summary that uses explicit methods to perform a comprehensive literature search, critically appraise it, and synthesize the world literature on a specific topic
2. Differs from a standard literature review: The study results do not include expert opinion and are more comprehensively synthesized and reviewed.
3. As with a randomized controlled clinical trial (or other studies), the key is a well-documented and well-described systematic review.

C. Meta-analysis

1. Systematic review that uses mathematical/statistical techniques to summarize the results of the evaluated studies

2. These techniques may improve on the following:
 - a. Calculation of effect size
 - b. Increase in statistical power
 - c. Interpretation of disparate results
 - d. Reduction in bias
 - e. Answers to questions that may not be addressable with individual studies
3. Reliant on criteria for inclusion of previous studies and statistical methods to ensure validity. Details of included studies are essential.
4. Elements of trial methodology
 - a. Research question
 - b. Identification of available studies
 - c. Criteria for trial inclusion/exclusion
 - d. Data collection and presentation of findings
 - e. Calculation of summary estimate: Ideally with forest plot (Figure 7). A forest plot illustrates heterogeneity and the pooled results of meta-analysis but not publication bias, which can be expressed in a funnel plot.
 - f. Assessment of heterogeneity
 - i. Statistical heterogeneity
 - ii. Chi-square and Cochran Q are common tests for heterogeneity.
 - iii. Assessment of publication bias:
 - (a) Funnel plot is a graph designed to check for the existence of publication bias commonly used in systematic reviews and meta-analyses.
 - (b) In the absence of publication bias, it assumes that the largest studies will be plotted near the average, and smaller studies will be spread evenly on both sides of the average, creating a roughly funnel-shaped distribution.
 - (c) Deviation from this shape can indicate publication bias
 - iv. Sensitivity analysis

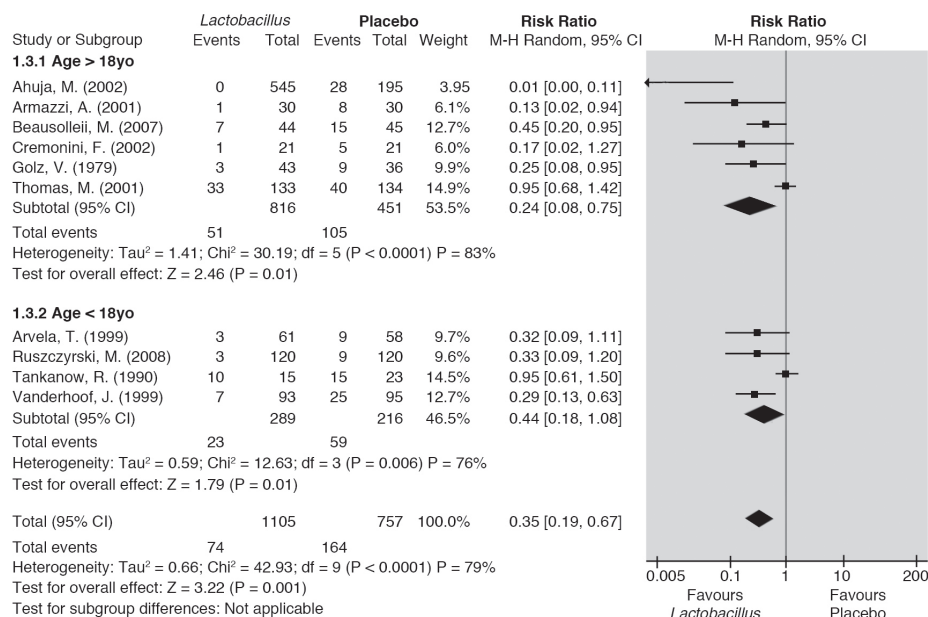


Figure 7. Forest plots.

CI = confidence interval; yo = years old.

From: Kale-Pradhan PB, Jassal HK, Wilhelm SM. Role of Lactobacillus in the prevention of antibiotic-associated diarrhea: a meta-analysis. *Pharmacotherapy* 2010;30:119-26.

D. Meta-analysis: Additional example (Arch Intern Med 2008;168:687-94)

XI. SUMMARY MEASURES OF EFFECT

A. Absolute and Relative Differences

1. Absolute differences or absolute changes
2. Relative differences or relative changes (i.e., ratio)
3. Absolute differences are more important than relative differences, although the authors of many clinical studies highlight the differences observed in trials with relative differences because they are numerically larger. Why? Larger numbers are more convincing to practitioners and patients. Most drug advertisements (directed both to patients and to health care professionals) quote relative differences.

B. Number Needed to Treat (NNT)

1. Characteristics

- a. Another means to characterize changes or differences in absolute risk
- b. Definition: The reciprocal of the absolute risk reduction (ARR)
 - i. $NNT = 1/(ARR)$.
 - ii. Rounded to the next highest whole number is the most conservative approach
- c. Applied to clinical outcomes with dichotomous data (e.g., yes/no, alive/dead, MI/no MI)
- d. Caution: Assumes the baseline risk is the same for all patients (or that it is unrelated to RR)
- e. Must consider the time interval of the study used to calculate the value
- f. NNTs should be provided only for statistically significant effects
- g. Number needed to harm can be calculated similarly for adverse events.

2. NNT application (Table 7)

- a. HOPE (Heart Outcomes Prevention Evaluation) study (Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 2000;342:145-53)
- b. Study evaluated the effect of ramipril on cardiovascular events in high-risk patients.
- c. Prospective randomized double-blind study
 - i. 9297 high-risk patients received ramipril or matching placebo once daily for an average follow-up of 5 years.
 - ii. Primary outcome: Composite of MI, stroke, or death from cardiovascular causes
- d. Results: $NNTs = 1/(0.178 - 0.140) = 1/0.038 = 26.3$, rounded up to 27.
- e. ARR meaning: Ramipril decreases risk of composite cardiovascular outcome by 3.8%.
- f. NNT meaning: 27 patients need to be treated with ramipril to prevent one composite cardiovascular outcome.

Table 7. Risk of Primary and Secondary End Points by Treatment Group

Outcome	Ramipril, %	Placebo, %	Relative Risk	RRR	ARR	NNT
Combined	14.0	17.8	0.78	0.21	0.038	27
Death from CV causes	6.1	8.1	0.74	0.25	0.02	50
Myocardial infarction	9.9	12.3	0.80	0.20	0.024	42
Stroke	3.4	4.9	0.68	0.31	0.015	67

ARR = absolute risk reduction; CV = cardiovascular; NNT = number needed to treat; RRR = relative risk reduction.

XII. REPORTING GUIDELINES FOR CLINICAL STUDIES

- A. The Consolidated Standards of Reporting Trials (CONSORT)
 - 1. Initially published in 1996 and updated several times – most recently, in 2010
 - 2. Created in an effort to improve, standardize, and increase the transparency of the reporting of clinical trials and to facilitate the improvement of literature evaluation
 - 3. Available at www.consort-statement.org/
 - 4. The CONSORT statement has been endorsed by several publications and published in these journals.
 - 5. The CONSORT statement
 - a. The checklist: 25-item checklist pertaining to the content of the following:
 - i. Title
 - ii. Abstract
 - iii. Introduction
 - iv. Methods
 - v. Results
 - vi. Discussion
 - vii. Other information
 - b. The flow diagram: Intended to depict the passage of study participants through the randomized controlled trial
 - 6. Extensions of the CONSORT statement
 - a. Design extensions
 - i. Cluster trials
 - ii. Noninferiority and equivalence trials
 - iii. Pragmatic trials
 - b. Intervention extension
 - i. Herbal medicinal interventions
 - ii. Nonpharmacologic interventions
 - iii. Acupuncture interventions
 - c. Data extensions
 - i. Patient-reported outcomes
 - ii. Harms
 - iii. Abstracts
- B. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement
 - 1. Initially published in 2007
 - 2. “An international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies”
 - 3. Available at stroke-statement.org
 - 4. Endorsed by a growing number of publications and published in these journals
 - 5. The STROBE checklist: 22-item checklist, same basic concepts as the CONSORT checklist, with alterations germane to observational trials
- C. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)
 - 1. Established in 1996 (as QUOROM), renamed in 2009
 - 2. Evidence-based minimum set of items for reporting systematic reviews and meta-analyses
 - 3. Available at prisma-statement.org
 - a. The PRISMA checklist: 27-item checklist with modifications germane to systematic reviews and meta-analyses

- b. The PRISMA flow diagram: Four-stage diagram, depicting the flow of information through the systematic review
 - c. The PRISMA explanation and elaboration document: Intended to enhance the use and understanding of the PRISMA statement
- D. Enhancing the Quality and Transparency of Health Research (EQUATOR) Network
 - 1. International initiative to improve the reliability and value of medical research literature by promoting transparent and accurate reporting of research studies
 - 2. Available at www.equator-network.org
 - 3. Does not have its own statements, but promotes the use of key reporting guidelines
 - 4. Many other statements regarding study types not addressed in the discussion related to CONSORT, STROBE, and PRISMA are listed on the EQUATOR network website.

XIII. PHARMACOECONOMIC STUDIES

- A. Cost-Minimization Analysis
 - 1. Differences in cost among comparable therapies are evaluated
 - 2. Only useful to compare therapies that have similar outcomes
- B. Cost-Effectiveness Analysis
 - 1. Outcome: Clinical units or cost per unit health outcome (outcome examples: years of life saved, number of symptom free days, etc.)
 - 2. Useful to measure the cost impact when health outcomes are improved
- C. Cost-Utility Analysis
 - 1. Assigns utility weights to outcomes so the impact can be measured in relation to cost (outcome example: quality-adjusted life-years)
 - 2. Compares outcomes related to mortality when mortality may not be the most important outcome
- D. Cost-Benefit Analysis
 - 1. Monetary value is placed on both therapy costs and beneficial health outcomes.
 - 2. Allows analysis of both the cost of treatment and the costs saved with beneficial outcomes

XIV. SENSITIVITY/SPECIFICITY/PREDICTIVE VALUES

- A. Sensitivity: Proportion of true positives that are correctly identified by a test; a test with a high sensitivity means that a negative test can rule OUT the disease
- B. Specificity: Proportion of true negatives that are correctly identified by a test; a test with high specificity means that a positive test can rule IN the disease
- C. Positive Predictive Value: Proportion of patients with a positive test result who actually HAVE the disease
- D. Negative Predictive Value: Proportion of patients with a negative test result who actually DO NOT HAVE the disease

E. Example: Tables 8 and 9

Table 8. Relationship Between Test and Correct Diagnosis Identified by Disease

	Disease		
Test	Disease Present	Disease Absent	Total
Test positive	True positive (TP)	False positive (FP)	TP + FP
Test negative	False negative (FN)	True negative (TN)	TN + FN
Total	TP + FN	FP + TN	Total

1. Sensitivity = $TP / (TP + FN)$
2. Specificity = $TN / (TN + FP)$
3. Positive predictive value = $TP / (TP + FP)$
4. Negative predictive value = $TN / (TN + FN)$
5. Positive likelihood ratio = $sensitivity / (1 - specificity)$
6. Negative likelihood ratio = $(1 - sensitivity) / specificity$

Table 9. Relationship Between Test and Correct Diagnosis Identified by Disease in a Published Study

	Disease		
Test	Positive disease	Negative disease	Total
Positive	231 (true positive)	32 (false positive)	263
Negative	27 (false negative)	54 (true negative)	81
Total	258	86	344

From: Drum DE, Christacopoulos JS. Hepatic scintigraphy in clinical decision making. J Nucl Med 1972;13:908-15.

XV. INSTITUTIONAL REVIEW BOARD (RB) AND HUMAN SUBJECTS' RESEARCH**A. Definitions**

1. Research: "Systematic investigation (i.e., research development, testing, and evaluation) designed to develop or contribute to generalizable knowledge"
2. Human subject: "Living individual about whom an investigator obtains data through intervention or interaction with the individual OR identifiable private information"
3. Quality improvement versus research
 - a. In general, if the results of a project are presented outside an organization (i.e., contributing to generalized knowledge), either as a publication or a presentation, it is defined as research.
 - b. If the results of a project are to be used internally and are not meant to contribute to generalized knowledge, the activities will fall under quality improvement. Ideally, the IRB makes this decision.

B. History and Development of Research Ethics

1. Nuremberg Code (1947)
 - a. Subjects should give informed voluntary consent
 - b. The benefits of research must outweigh the risks
2. Declaration of Helsinki (1964)
 - a. Governs international research ethics for medical research involving human subjects
 - b. Defines rules for "research combined with clinical care" and "nontherapeutic research"
 - c. Basis for good clinical practices used today

3. Tuskegee Syphilis Study (1972)
 - a. The study did not minimize risks to human subjects. In fact, it increased their risks.
 - b. These issues heightened awareness of the need to protect human subjects and to ensure their informed voluntary consent.
4. Belmont Report (1979): Prepared by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
 - a. Summarizes the basic ethical principles identified in its deliberations: respect for persons, beneficence, and justice
 - b. Serves as a statement of basic ethical principles and guidelines that assist in resolving the ethical problems that surround the conduct of research with human subjects
5. Code of Federal Regulations (CFR) (1981): The Department of Health and Human Services (DHHS) and the U.S. Food and Drug Administration (FDA) issued regulations according to the Belmont Report:
 - a. DHHS: CFR Title 45 (public welfare), Part 46 (protection of human subjects)
 - b. FDA: CFR Title 21 (food and drugs), Parts 50 (protection of human subjects) and 56 (IRBs)
6. Common Rule (1991)
 - a. Obtaining and documenting informed consent
 - b. IRB membership, function, operations, review of research, and recordkeeping
 - c. Additional protections for certain vulnerable research subjects: Pregnant women, fetuses, prisoners, children, individuals with impaired capacity
 - d. Ensuring compliance by research institutions. All institutions that conduct federally sponsored research must provide the federal government “assurance” that states the institution’s principles for protecting the rights and welfare of human subjects.
7. IRB review of studies: Reviewed at one of three levels, depending on the level of risk to the human subjects. The federal guidelines that define the categories of review, which are as follows:
 - a. Exemption from full IRB review
 - i. Categories (Table 10)
 - (a) Research conducted in established or commonly accepted educational settings
 - (b) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior unless the subject can be identified
 - (c) Research involving the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects
 - (d) Research and demonstration projects that are conducted by or subject to the approval of department or agency heads
 - ii. Projects are not assigned an expiration date.
 - iii. The IRB makes the final decision on exemption; a staff member usually reviews the proposal.
 - iv. Review usually takes a few days.
 - b. Expedited IRB review
 - i. Minimal risk to participant
 - ii. Minor change to previously approved study
 - iii. Chairperson or designee reviews the proposal
 - iv. Review usually takes a few weeks
 - c. Full IRB review:
 - i. More than minimal risk
 - ii. Review protocol and supporting documents
 - iii. Lengthy process, usually months
 - iv. Full IRB board members review the proposal

Table 10. Examples of IRB Review Categories

Type of Review	Examples
Exemption from review	Epidemiologic study with NHANES data Study of changes in the number of days requiring antibiotics, using de-identified institutional data
Expedited review	Cross-sectional study of patients with heart failure measuring a biomarker, requiring a single blood sample Case-control study of the relationship between admission to the hospital and drug use
Full review	Randomized controlled trial of a new drug or device for heart failure therapy Cross-sectional study requiring bronchoscopy after administration of methacholine

IRB = institutional review board; NHANES = National Health and Nutrition Examination Survey.

8. IRB composition

- a. At least five members
 - i. Chairperson
 - ii. Scientific member
 - iii. Nonscientific member
 - iv. Layperson unaffiliated with the institution
 - v. Practitioner
- b. Sufficient qualifications through the experience, expertise, and diversity of its members and backgrounds, including considerations of their racial and cultural heritage and their sensitivity to issues such as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects
- c. Membership must be able to ensure protection of vulnerable populations.
- d. Membership must come from more than one profession.

9. Informed consent

- a. Informed consent is a process, not a form. Information must be presented to the individual (or representative) to enable that person to make a voluntary decision to participate as a research subject.
- b. Components
 - i. Description of any reasonably foreseeable risks or discomforts
 - ii. Description of any benefits to the subject or to others that may reasonably be expected
 - iii. Disclosure of appropriate alternative procedures or courses of treatment, if any
 - iv. Statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained
 - v. For research involving more than minimal risk, an explanation about whether any compensation and an explanation about whether any medical treatments are available if injury occurs
 - vi. Contact information for answers to questions about the research and research subjects' rights; whom to contact if the subject has a research-related injury
 - vii. A statement that participation is voluntary; refusal to participate will involve no penalty or loss of benefits, and the subject may discontinue participation at any time without penalty
 - viii. Assent is a process required for children or adults lacking the capacity to give informed consent. It ensures these subjects understand the research and what it means to participate.
- c. Waiver or alteration of consent: An IRB may waive/alter informed consent if the following are met:
 - i. No more than minimal risk
 - ii. Will not adversely affect the rights and welfare of the subjects
 - iii. The research could not practicably be carried out without waiver.
 - iv. Subjects will be provided additional pertinent information after participation.

- d. An IRB may also waive informed consent in a limited class of research in emergency settings (e.g., life-threatening situations in which available treatments may be “unproven or unsatisfactory”) and when obtaining informed consent is not feasible.

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ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: B**

Recall bias is always a potential concern in case-control studies because of the time that passes between the study and the drug administration (Answer B is correct). Patients who develop adverse events are more likely to recall their exposures than are patients who did not have adverse events. Although a study may be susceptible to many types of bias, the other choices would not pose as much risk (if any) as recall bias, given the information provided about the study (Answers A, C, and D are incorrect). Having trained interviewers reduces the risk of interviewer bias, a data monitoring committee reduces the risk of misclassification bias, and having similar rates of risk factors for infusion-related reactions decreases the risk of selection bias.

2. Answer: B

Internal validity is jeopardized by the high risk of recall bias. The researcher's ability to properly identify the rates of exposure to the new immune globulin product will be affected by how well the patients recall being exposed to the product (Answer B is correct). External validity deals with the generalizability of the results outside the study setting. There is no indication of a threat to external validity in this question (Answer A is incorrect). This question refers to a case-control study, and randomization is not involved (Answer C is incorrect); recall bias will not affect study recruitment (Answer D is incorrect).

3. Answer: B

Intention-to-treat analyses generally best estimate effectiveness (intervention use under real-world conditions), whereas per-protocol analyses better estimate efficacy (intervention use under ideal conditions) (Answer B is correct; Answer C is incorrect). Intention-to-treat analysis is the most common approach to data analysis for randomized controlled trials and may underestimate the treatment effect (Answer D is incorrect). Recall bias is not a concern with randomized controlled trials (Answer A is incorrect).

4. Answer: B

The CI of the difference in hospitalization rates between the two groups includes zero; thus, there is no statistically significant difference between the two groups (Answer B is correct). Answer A is incorrect because

the 95% CI contains zero and is therefore not statistically significant. Answer C is incorrect because not enough information is provided to determine whether the criteria for noninferiority have been met. Answer D is incorrect because all the above information can be determined without the benefit of reported p values.

5. Answer: D

Answers A and C are incorrect calculations. The NNT to prevent one hospitalization using twice-daily therapy is calculated as follows: $0.044 - 0.029 = 0.015$ and $1/0.015 = 66.7 \dots 67$; however, the NNT should not be calculated when the end point of interest is not significantly different from the comparator (Answer B is incorrect; Answer D is correct).

6. Answer: C

Answers A and B are incorrect because the ketogenic diet did not significantly reduce the risk of seizures (the 95% CI includes 1 [no difference in risk]). Answer D is incorrect because the p value is not required to interpret statistical significance when the 95% CI is provided. Answer C is correct because the p value corresponds to the 95% CI.

7. Answer: A

Clinical trials are usually adequately powered to compare primary end points (Answer A is correct). Because Answer B is part of the composite outcome, the study was likely not powered to detect this outcome independently. Similarly, even though the subgroup analysis was determined a priori, the study is not typically designed to have sufficient power to make this comparison (Answers C and D are incorrect).

8. Answer: D

Answers A and B are incorrect because each implies that one drug is more effective than the other. For observational studies, causality cannot truly be assessed. In this type of study design, neither drug is more/less effective. Answer C is incorrect because the CI of the OR does not include 1; thus, the finding is statistically significant at the 5% level, making Answer D correct.

9. Answer: A

Federal law guidance for IRB membership simply states that membership must include at least five individuals:

a chairperson, a scientific member, a nonscientific member, a layperson unaffiliated with the institution, and a practitioner (Answer A is correct). There is no requirement for size of membership or a certain number of individuals (Answers B and C are incorrect) or for a physician (Answer D is incorrect).

10. Answer: B

Answer A is incorrect because information related to how research participants were selected should be in the methods. The results and summary of previous studies appear in the study's introduction to frame the objective of the current study or in the discussion to relate the results of the current study to the results of other studies (Answer B is correct). Answer C is incorrect because this information should be in the results section. Answer D is incorrect because acknowledgments should be in the acknowledgments section.

MEDICATION SAFETY

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Learning Objectives

1. Identify common medication safety events and risk factors in pediatric patients.
2. Analyze and address medication safety events in your organization.
3. Identify and evaluate error reduction strategies that could be used to address pediatric medication errors in your organization.

Self-Assessment Questions

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

1. You are a pharmacist member of your organization's Medication Safety Committee. To achieve the goal of eliminating harm from medications, the committee must begin with identification of harm events. Which best depicts the organization that provides a standard for the scoring and classification of medication safety events?
 - A. Institute for Safe Medication Practices (ISMP).
 - B. The Joint Commission.
 - C. National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP).
 - D. Institute of Medicine (IOM).
2. Which error reduction strategy most lacks primary literature supporting a decrease in medication safety events in pediatric patients?
 - A. Barcode medication administration.
 - B. Smart pump infusion technology.
 - C. Two-clinician independent double-check.
 - D. Computerized physician order entry.
3. You are the pharmacist on a team completing a root-cause analysis of a serious medication safety event in which a patient with acute kidney injury was harmed after a dosing error with foscarnet. When reviewing the action items to address the system vulnerabilities, which error reduction strategy would offer the greatest potential to reduce medication errors in pediatric patients?
 - A. At the next staff meeting, educate pharmacist staff on the appropriate dose adjustments needed for patients with acute kidney injury.
 - B. Create a policy for using foscarnet in patients with acute kidney injury, and communicate it in the pharmacy and therapeutics newsletter.
 - C. Create a checklist to be used by the pharmacist when verifying new orders for foscarnet to ensure renal function is checked before dosing.
 - D. Update the drug record in the computerized physician order entry (CPOE) system to require the foscarnet dose calculation to include the patient's CrCl.
4. You are a pharmacist member of your organization's Medication Safety Committee. To achieve the goal of eliminating harm from medications, the committee must first identify harm events. Which mechanism to detect harm has best been shown to provide the highest yield?
 - A. Voluntary reporting.
 - B. Continuous quality improvement data from smart infusion pumps.
 - C. Continuous quality improvement data from barcode medication administration.
 - D. Adverse drug event (ADE) trigger tool methodology.
5. You are a clinical pharmacist walking onto your unit in preparation for rounds. In reviewing your list of patients, which patient scenario would be most at risk for an ADE occurring?
 - A. A neonate receiving ciprofloxacin for treatment of a resistant *Escherichia coli* bacteremia.
 - B. An 8-year-old patient with cystic fibrosis receiving dornase alfa for maintenance of lung function.
 - C. A 12-year-old patient receiving prednisolone and albuterol for management of an asthma exacerbation.
 - D. A 16-year-old female adolescent receiving ciprofloxacin for management of an *E. coli* urinary tract infection.
6. Which pediatric liquid ambulatory prescription for a patient weighing 20 kg has the highest potential for error?
 - A. Amoxicillin 250 mg/5 mL – Give 16 mL (800 mg) by mouth twice a day for 7 days.
 - B. Famotidine 8 mg/mL – Give 2.5 mL (20 mg) by mouth once a day.

-
- C. Captopril 1 mg/ mL – Give 6 mL (6 mg) by mouth every 8 hours.
- D. Furosemide 10 mg/ mL – Give 1 mL (10 mg) by mouth twice a day.
7. Barcoding medications at the point of administration has been shown to reduce medication safety events. Which most likely poses a unique challenge to implementing effective barcoding in pediatric patients?
- Limiting workarounds and increasing scanning compliance.
 - Using National Drug Code numbers as the medication identifier because limited by the degree of medication manipulation.
 - Ensuring that all manufacturer preparations have readable and accessible barcodes.
 - Providing clinicians accessibility to computers and scanners in their workflow.
8. Off-label medication use is commonly referenced as a risk factor for ADEs in pediatric patients. Which statement best describes off-label medication use in children?
- Considered experimental and requires investigational consent before use.
 - May not account for differing pharmacokinetic parameters in pediatric patients.
 - Should be avoided because of the unknown risk of ADEs.
 - Unsupported by clinical experience or scientific evidence for safe use in children.
9. You are a pharmacist on the Medication Safety Committee. Your organization has asked you to benchmark your medication safety error rate with that of similar pediatric organizations. Which is the most appropriate response?
- Given the limitations of voluntary reporting, it is impossible to compare medication safety error rates across different organizations.
 - Collect the medication serious safety event rate from five comparable organizations.
 - Collect the medication near-miss safety event from five comparable organizations.
 - Collect the pharmacist prescribing intervention rate from five comparable organizations.
10. Voluntary reporting systems are paramount for health care organizations to identify potential safety vulnerabilities. Which is the most accurate statement regarding voluntary reporting systems?
- They are effective in defining a patient safety event rate within an organization.
 - A nonpunitive response to reporting is vital to optimize reporting.
 - Primary literature shows that 80% of all safety events are captured by voluntary reporting systems.
 - Voluntary reporting systems are equivalent to trigger tools in detecting patient safety events causing harm.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:
Domain 2: Practice Management and Medication Safety; Task(s): 2.1, 2.2, 2.5, 2.6, 2.7

I. MEDICATION SAFETY

A. Introduction

1. The IOM reports on patient safety events in the health care system.
 - a. *To Err Is Human* (1999)
 - i. 44,000–98,000 people die in hospitals each year as a result of medical errors.
 - ii. \$17–29 billion per year in additional costs related to medical errors
 - iii. Errors are caused by faulty systems, processes, and conditions.
 - b. *Crossing the Quality Chasm* (2001): Identified the six aims of improvement in care to ensure that care is safe, effective, patient-centered, timely, efficient, and equitable
 - c. *Preventing Medication Errors* (2006)
 - i. Medication errors are most common during the prescribing and administration phases of the medication process.
 - ii. 1.5 million preventable ADEs occur in the United States per year.
 - iii. The following are recommended error reduction strategies: encouraging patients to become more active in their care, leveraging technology (i.e., electronic health records, smart infusion pumps, barcoding medication administration), and improving the labeling and packaging of medications.
2. Landmark pediatric medication safety events
 - a. 2001: Josie King, an 18-month-old girl, dies of severe dehydration and narcotic overdose.
 - b. 2006: Emily Jerry, a 3½-year-old girl, dies when her chemotherapy is diluted in 23.4% sodium chloride instead of 0.9%.
 - c. 2006: Three premature neonates die after receiving heparin 10,000 units/mL rather than the intended 10 units/mL.
 - d. 2011: An 8-month-old dies in an intensive care unit after receiving 1400 mg of calcium chloride instead of the intended 140 mg.

B. Definitions

1. Many definitions exist for medication safety terminology, but there are no standard definitions among organizations, researchers, or safety professionals.
2. Medication error:
 - a. According to the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), medication errors:
 - i. Are any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the health care professional, patient, or consumer.
 - ii. May be related to:
 - (a) Professional practice
 - (b) Health care products
 - (c) Procedures and systems, including prescribing, order communication, product labeling, packaging, nomenclature, compounding, dispensing, distribution, administration, education, monitoring, and use
 - b. Not all medication errors result in ADEs. Those that do not result in harm are called “near miss” events.
3. NCC MERP provides a medication error index for categorizing medication errors according to the severity of the outcome.

NCC MERP Index for Categorizing Medication Errors

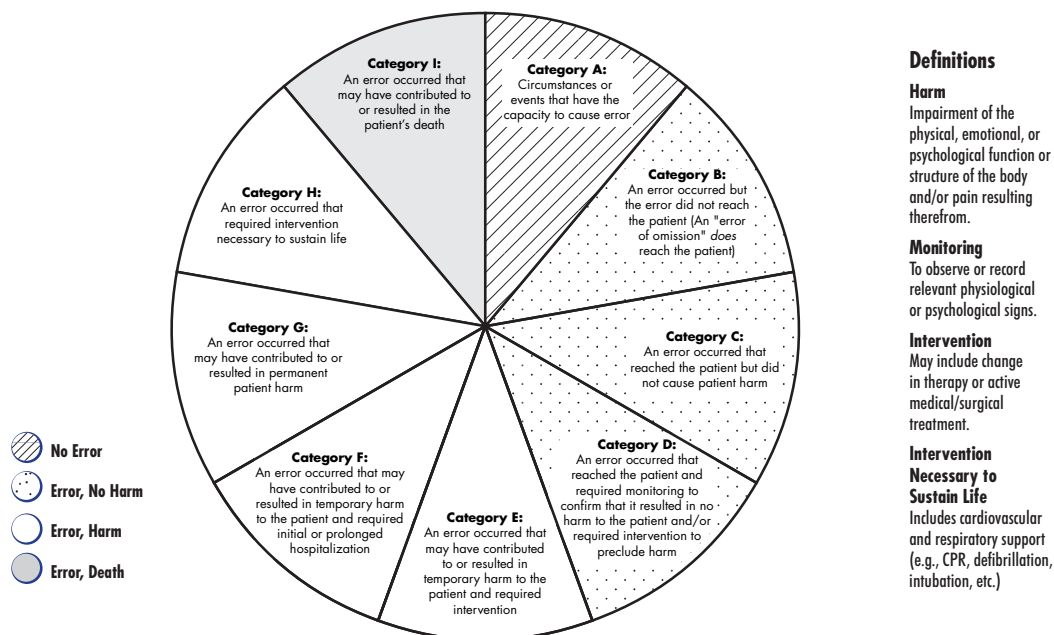


Figure 1. NCC MERP index for categorizing medication errors.

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4. Adverse drug events (ADEs):
 - a. Harm caused by use of a drug
 - b. ADEs are not necessarily the result of a medication error.
 - c. Preventable ADEs include harm caused by use of a drug resulting from an error.
 - d. Non-preventable ADEs include harm caused by appropriate use of a medication and do not involve a medication error.
5. Adverse drug reactions (ADRs):
 - a. Patients may experience harm from use of a medication even when it is prescribed and administered appropriately. These events are called ADRs, adverse effects, or non-preventable ADEs. Some definitions for ADRs continue to be more inclusive and similar to the general ADE definition.
 - b. All ADRs fall under the definition of ADE.
 - c. The American Society of Health-System Pharmacists defines an ADR as any unexpected, unintended, or excessive response to a drug that requires or results in:
 - i. Discontinuation of the drug (therapeutic or diagnostic)
 - ii. Change in drug therapy
 - iii. Modification of the dose (except for minor dose adjustments)
 - iv. Admission to a hospital
 - v. Prolonged stay in a health care facility
 - vi. Supportive treatment
 - vii. Significant complications in diagnosis
 - viii. Negative effects on prognosis
 - ix. Temporary or permanent harm, disability, or death
 - d. The World Health Organization defines an ADR as any response to a drug that is noxious and unintended, which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or modification of physiological function.

Patient Cases

Questions 1 and 2 pertain to the following case.

N.T. is a 10-year-old boy (weight 32 kg) admitted to the surgical inpatient unit after sustaining a femur fracture during a motor vehicle accident. He received a 4-mg intravenous dose of morphine in the postanesthesia care unit. The patient was transferred to the floor, where he received a 2-mg morphine intravenous dose 15 minutes after the last dose. Shortly after the dose was administered, he became apneic and required naloxone and bag/mask ventilation. The patient returned to his baseline 10 minutes later.

1. Which best defines this event?
 - A. Near-miss event.
 - B. ADE.
 - C. ADR.
 - D. Both an ADR and an ADE.
2. Which NCC MERP classification best categorizes this event?
 - A. Category A.
 - B. Category B.
 - C. Category E.
 - D. Category I.

C. Pediatric Medication Error Incidence

1. The incidence of medication errors in pediatric patients has been reported as 5.7 per 100 medication orders.
2. 79% of potential ADEs occur during the prescribing phase.
3. The incidence of preventable ADEs has been reported to be up to 74 per 1000 patient-days.
4. Up to 15.2% of medication errors result in a preventable ADE.
5. Most preventable ADEs in pediatric patients have been reported as minor harm.
6. The most common drug classes include intravenous antibiotics, electrolytes and fluids, and analgesics and sedatives.
7. The most common types of errors were improper dose or quantity (37.5%), omission errors (19.9%), unauthorized or wrong drug (13.7%), and prescribing error (9.4%).
8. The rate of potential ADEs is 3 times higher for pediatric patients.
9. Neonatal patients are at highest risk of potential ADEs.
10. Around 200,000 children annually experience ADEs requiring an ED visit, with those younger than 5 years more likely to have this experience.

D. Pediatric-Specific Risk Factors for Medication Errors and Harm

1. Developmental pharmacokinetics
 - a. Greater volume of distribution than adults, most notably in neonates and infants
 - b. Lower concentration and affinity of drug-binding proteins
 - c. Variable enzymatic capacity affecting drug metabolism and metabolism of inactive ingredients
 - d. Delayed renal elimination in neonates
 - e. Limited physiologic buffering to recover from medication errors

2. Weight-based dosing: Weight- or body surface area–based dosing increases the need for calculation of individualized doses and potential for error.
3. Off-label use of medications
 - a. Legislation intended to decrease off-label use of medications in pediatric patients:
 - i. Best Pharmaceuticals for Children Act (BPCA) 2002
 - ii. Pediatric Research Equity Act (PREA) 2003
 - b. Off-label medication use refers to use of a drug that is not included in the package insert for that drug. Off-label include uses outside of approved:
 - i. Age
 - ii. Indication
 - iii. Weight
 - iv. Dose
 - v. Formulation
 - vi. Route of administration
 - c. Rates of off-label use vary widely in the literature and among practice settings, patient populations, drug classes, and specialty practices.
 - i. Overall: 3.2%–95%
 - ii. Inpatient care: 54%–80%
 - iii. Observational: 45%
 - iv. Ambulatory care: 45%–65%
 - v. Pediatric intensive care: 85%
 - vi. Emergency medicine: 10%
 - d. Primary literature suggests that the following patient factors and outcomes are associated with an increased likelihood of off-label medication use:
 - i. Younger age, especially those younger than 1 year
 - ii. Longer hospital stay
 - iii. Mortality
 - iv. Disease severity
4. Communication barriers:
 - a. Preverbal and nonverbal patients cannot communicate about potential adverse events.
 - b. Varying ability to recognize and speak up about a potential medication error
 - c. Clinician and caregiver assessments may be used to assess for effectiveness and adverse events.
 - d. Reliance on caregiver for accurate medication use
 - e. Health literacy of patient and caregiver must be considered.
 - f. Potential for multiple caregivers
5. Lack of appropriate drug formulations
 - a. Suspensions, solutions, and other dosage forms and concentrations needed for appropriate pediatric dosing and administration are often not commercially available.
 - b. Extemporaneously prepared oral suspensions
 - i. Alteration of commercially available products can affect bioavailability, stability, and sterility.
 - ii. Many recipes for extemporaneous compounding may exist for the same medication, which creates the potential for medication errors across the care continuum.
 - iii. All compounding recipes should be based on peer-reviewed sources.
 - c. Intravenous medication manipulation: The need for dilution can increase the risk or potential for error.

- d. Standardize the concentrations used for enteral and intravenous medications.
 - i. Use state or national standards for selecting standard concentrations when available.
 - ii. Decrease the number of standard concentrations available for use to the minimum necessary for appropriate medication delivery to patient populations served.
- e. Examples of appropriate references for intravenous dilutions and extemporaneously compounded preparations
 - i. Jew RK, Soo-Hoo W, Amiri E, et al. Extemporaneous Formulations for Pediatric, Geriatric, and Specials Needs Patients, 4th ed. Bethesda, MD: American Society of Health-System Pharmacists, 2021.
 - ii. Phelps SJ, Hagemann TM, Lee KR, et al. Pediatric Injectable Drugs 11th Edition (The Teddy Bear Book). American Society of Health-System Pharmacists, 2018.
 - iii. American Society of Health-System Pharmacists. Standardize 4 Safety Initiative: Standard 4 Safety Resources. Available at www.ashp.org/pharmacy-practice/standardize-4-safety-initiative#s4sresources.
6. Use and availability of appropriate measurement devices
 - a. Oral or enteral syringes meeting International Organization Standardization (ISO) standards or properly marked dosing cups should be used.
 - i. Dispense unit dose oral liquid medications that are not commercially available in oral or enteral syringes from the pharmacy.
 - ii. Do not stock bulk oral solutions of medication on patient care areas.
 - iii. If using ISO 80369 compliant enteral syringes for oral medication administration, include an auxiliary warning on the syringe or label to indicate “For Oral Use Only” to prevent a wrong route error.
 - b. Use metric system units, when possible.
 - c. Use appropriate syringe size to account for accuracy of smallest measurable dose in the syringe; for example, draw up doses no smaller than 20% of the capacity of the syringe.
 - d. Create dilutions for medications when necessary in order to accurately measure the dose using appropriate measuring devices.

Patient Case

3. A pharmacist receives a prescription for captopril 6.25 mg by mouth every 8 hours for a 2-year-old girl (weight 15 kg) for management of her hypertension. The patient cannot take tablets or pills, and the family asks about a liquid formulation. Which is the most appropriate next step?
 - A. Review the primary literature to determine whether a recipe with stability data exists.
 - B. Consult with the prescriber to determine if a therapeutic alternative commercially available product in a pediatric formulation is suitable for substitution.
 - C. Instruct the family to dissolve a 12.5-mg tablet in 2.5 mL of Ora-Sweet and 2.5 of Ora-Plus, and administer 2.5 mL every 8 hours.
 - D. Instruct the family to dissolve a 12.5-mg tablet in 5 mL of water, and administer 2.5 mL every 8 hours.

E. Strategies for Error and Harm Detection, Measurement, and Improvement Methods

1. Voluntary reporting
 - a. Detects ADEs, medication errors, and safety risks that those involved in the medication use process identify and report in the system
 - b. Voluntary reporting systems may capture 5%–20% of adverse events that are actually occurring.

- c. Provides greater yield than mandatory reporting systems because of the perceived lack of retribution
- d. The depth of information contained in error reports leads to outcomes that are more productive.
- e. Voluntary reporting systems can be limited by the following:
 - i. Perceived punitive response from colleagues and leaders
 - ii. Poorly designed or arduous reporting systems
 - iii. Lack of awareness that an error occurred
 - iv. Lack of time during regular staffing hours to report the errors
 - v. Lack of time for review and follow up on reported events
2. ADE trigger tool method
 - a. Use of triggers in the medical record to identify possible adverse events
 - i. Triggers may be detected through a retrospective manual review of a random sample of inpatient hospital records.
 - ii. Triggers may be detected through an automated report from the electronic health record.
 - b. The trigger tool method captures more than 10 times as many detected patient safety events as voluntary reporting with little overlap between the two detection methods.
 - c. Although several studies have been published on pediatric triggers, development of consensus pediatric-specific triggers is still needed.
3. Continuous quality improvement data from technology (e.g., barcoding, smart pumps)
 - a. Allows capture of compliance with medication use processes
 - b. Identification of errors intercepted by technology (e.g., good catches, near misses)
4. Direct observation of processes throughout the medication use system to detect errors, ADEs, and risk points
5. Metrics to consider for medication safety outcome and process monitoring
 - a. Preventable ADE rate
 - b. Non-preventable ADE rate
 - c. Medication error reporting rate
 - d. Barcode medication administration (BCMA) compliance rate
 - e. Smart pump drug library compliance
 - f. Overrides from automated dispensing cabinets
 - g. Pharmacy preparation and dispensing barcode scanning compliance
 - h. Process compliance from observational audits
6. Improvement methods
 - a. Proactive risk assessments to identify and evaluate potential errors and risk points
 - i. Failure Modes and Effects Analysis (FMEA)
 - ii. Gap analysis based on published literature or news reports
 - iii. Self-assessments provided by safety and regulatory organizations
 - b. Learning from data, events, and safety reports
 - i. Root-cause analysis for serious ADEs to understand system root causes
 - ii. Apparent cause analysis for less serious ADEs to understand system-proximate causes
 - iii. Common cause analysis to understand trends among several event analyses
 - iv. Continuous quality improvement data to identify errors intercepted by technology (e.g., good catches, near misses) and risk points for medication errors in clinical practice
 - c. Structured improvement methods to address causes through system design
 - i. Lean Six Sigma
 - ii. Model for Improvement
 - iii. Human factors engineering evaluations, design, and expertise
 - iv. Flow diagrams
 - v. Cause and effect diagrams
 - vi. PDSA (plan-do-study-act) cycles

F. Error and Risk Mitigation Considerations and Strategies

1. Resources for medication safety ideas, standards, and measures
 - a. ISMP
 - b. National Quality Forum
 - c. Centers for Medicare & Medicaid Services
 - d. Institute for Healthcare Improvement
 - e. American Academy of Pediatrics
 - f. The Joint Commission
 - g. Agency for Healthcare Research and Quality
 - h. FDA MedWatch
 - i. National Coordinating Council for Medication Error Reporting and Prevention
 - j. CDC
 - k. Publications and presentations
 - l. Private collaborations
 - m. American Society of Health System Pharmacists
2. Medication risk reduction strategies must be considered throughout the medication use system.
 - a. Systems should be designed to prevent errors from occurring and to make errors visible and minimize harm when they do occur.
 - b. Components of the medication use system include:
 - i. Procurement
 - ii. Prescribing/ordering
 - iii. Preparation and dispensing
 - iv. Administration
 - v. Monitoring
 - vi. Transitions of care: Admission, transfer, discharge
 - c. ISMP's key elements of the medication use system provide 10 components to use for evaluating the medication use system.

Table 1. ISMP's Key Elements of the Medication Use System

Component	Descriptions
Patient information	Essential information is obtained, readily available in useful form, and considered when prescribing, dispensing, and administering medications
Drug information	- Essential drug information is readily available in useful form and considered when ordering, dispensing, and administering medications - A controlled formulary system is established to limit choice to essential drugs, minimize the number of drugs with which practitioners must be familiar, and provide adequate time for designing safe processes for the use of new drugs added to the formulary
Communication of drug orders and other drug information	Methods of communicating drug orders and other drug information are standardized and automated to minimize the risk of error
Drug labeling, packaging, and nomenclature	- Strategies are undertaken to minimize the possibility of errors with drug products that have similar or confusing manufacturer labeling or packaging or have drug names that look or sound alike - Readable labels that clearly identify drugs are on all drug containers, and drugs remain labeled up to the point of administration

Table 1. ISMP's Key Elements of the Medication Use System (*continued*)

Component	Descriptions
Drug standardization, storage, and distribution	• Intravenous solutions, drug concentrations, doses, and administration times are standardized whenever possible • Medications are provided to patient care units in a safe and secure manner and available for administration within a time interval that meets essential patient needs • Unit-based floor stock is restricted • Hazardous chemicals are safely sequestered from patients and not accessible in drug preparation areas
Medication device acquisition, use, and monitoring	• The potential for human error is mitigated through careful procurement, maintenance, use, and standardization of devices used to prepare and deliver medications
Environmental factors, workflow, and staffing patterns	• Medications are prescribed, transcribed, prepared, dispensed, and administered in a physical environment that offers adequate space and lighting and allows practitioners to remain focused on medication use without distractions • The complement of qualified, well-rested practitioners matches the clinical workload without compromising patient safety
Staff competency and education	• Practitioners receive sufficient orientation to medication use and undergo baseline and annual competency evaluation of knowledge and skills related to safe medication practices • Practitioners involved in medication use are provided with ongoing education about medication error prevention and the safe use of drugs that have the greatest potential to cause harm if misused
Patient education	• Patients are included as active partners in their care through education about their medications and ways to avert errors
Quality processes and risk management	• A nonpunitive, system-based approach to error reduction is in place and supported by management, senior administration, and the board of trustees or directors • Practitioners are motivated to detect and report errors, and interdisciplinary teams regularly analyze errors that have occurred within the organization and in other organizations for redesigning systems to best support safe practitioner performance • Simple redundancies that support a system of independent double-checks or an automated verification process are used for vulnerable parts of the medication system to detect and correct serious errors before they reach patients • Proven infection control practices are followed when storing, preparing, and administering medications

Adapted with permission from: Institute for Safe Medication Practices (ISMP).

3. Select the strongest error and risk reduction strategies possible when developing and implementing mitigations.
 - a. Use several mitigation strategies targeted at different parts of the medication use system when designing systems for error prevention and risk reduction.
 - b. Rank the order of effectiveness of error reduction strategies (ISMP).

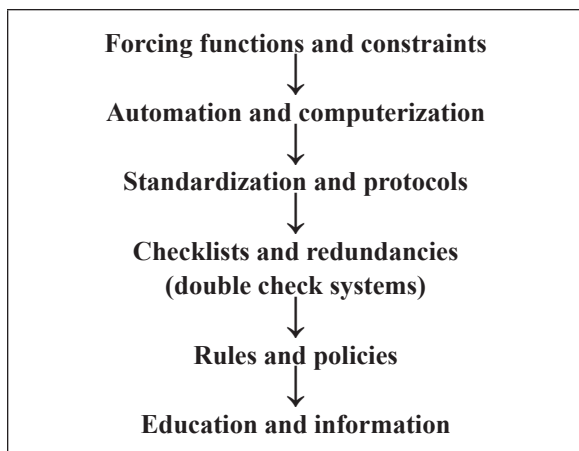


Figure 2. Rank order of error reduction strategies.

Adapted with permission from: Institute for Safe Medication Practices (ISMP).

- c. People-focused interventions include:
 - i. Education and information
 - ii. Rules and policies
 - iii. Checklists and redundancies
- d. System-focused interventions include:
 - i. Standardization and protocols
 - ii. Automation and computerization
 - iii. Forcing functions and constraints
- e. Additional error and risk mitigation concepts to consider:
 - i. Decrease reliance on memory
 - ii. Simplify
 - iii. Improve information access
 - iv. Reduce handoffs
 - v. Increase feedback
 - vi. Make it easy to do the right thing and hard to do the wrong thing

Patient Case

4. A.O. is an 18-month-old girl (weight 12 kg) admitted to the intensive care with head trauma and subsequent elevated intracranial pressure (ICP) after a motor vehicle accident. To control the ICP, A.O. is initiated on a sodium chloride 3% infusion at 5 mL/kg/hour. When initiating the infusion, the bedside nurse inadvertently programs the infusion pump at 50 mL/kg/hour. The infusion is initiated and runs for 15 minutes before the error is detected. Which error reduction strategy would be optimal to prevent future, similar errors?
 - A. Educate the nursing staff about the importance of completing the five rights of medication administration.
 - B. Implement a two-clinician independent double-check policy for all high-alert medications and include sodium chloride 3%.
 - C. Implement a pediatric-specific infusion pump library including hard stop limits for high-risk medications.
 - D. Write and implement a policy related to the administration of sodium chloride 3%.

4. Common causes of medication errors to mitigate
 - a. Failed communication
 - b. Poor drug distribution practices
 - c. Dose miscalculations
 - d. Drug- and drug device-related problems
 - e. Incorrect drug administration
 - f. Lack of patient education

- G. Error and Risk Mitigation Strategies
 1. Create a strong safety culture.
 - a. Safety culture helps us:
 - i. Eliminate fear and blame
 - ii. Promote teamwork
 - iii. Accept responsibility
 - iv. Learn, innovate, and engage in appreciative inquiry
 - v. Empower frontline workers
 - vi. Engage patients and families
 - b. Be transparent:
 - i. Share data
 - ii. Share safety stories
 - c. Develop a just culture:
 - i. Encourage staff to speak up when faced with risk or mistakes
 - ii. Reward reporting
 - iii. Value open communication between managers and staff
 - iv. Establish a system of shared accountability
 - v. Emphasize gaining knowledge and learning
 - vi. Recognize that although humans are fallible, we do generally have control over our behaviors
 - vii. Behaviors and errors:
 - (a) Human error
 - (1) Look for system weaknesses, and implement process or environmental changes to prevent future errors.
 - (2) Console and provide coping strategies staff involved in event.
 - (b) At-risk behavior
 - (1) Rewards of at-risk behaviors can become so common that perception of their risk fades or they are believed to be justified.
 - (2) Identify the system-based reasons for at-risk behavior, and decrease staff tolerance for risk-taking.
 - (3) Address incentives for at-risk behavior and coach staff on making better behavioral choices.
 - (c) Reckless behavior
 - (1) Behaviors are categorized as reckless when the worker realizes the possibility of harm, regardless of whether harm was intended or resulted.
 - (2) Health care providers rarely engage in reckless behavior. These behaviors may require disciplinary action.
 - d. Leadership practices
 - i. There must be no question of safety as the priority.
 - ii. Create a sense of urgency.
 - iii. Leaders are personally involved.
 - iv. Remove barriers to safety and break down silos.

- v. Eliminate hierarchical barriers.
- vi. Empower frontline workers through accountability and involvement.
- vii. Allow for quick decision-making in the face of risk.
- viii. Celebrate successes.
- e. Staff safety practices
 - i. Mindfulness, pause to care: Take a breath, slow down, focus on task or person
 - ii. Stop and resolve: Do not proceed in the face of uncertainty.
 - iii. Be open to being questioned and thank those who ask questions.
 - iv. Repeat back information you have received.
2. Communication tools to improve safety
 - a. Clear, concise communication
 - i. SBAR: Situation, background, assessment, recommendation
 - ii. Situational briefing
 - b. Critical language for concern escalation, CUS: concern, uncomfortable, safety
 - c. Assertion training
 - d. Awareness and education regarding communication challenges as root causes of error
 - e. Introduction of all team members to facilitate role understanding and open discussion
 - f. Structured handoffs during shift changes and with patient transfers
3. High-alert medication error reduction strategies
 - a. Develop a list of high-alert medications specific to your location on the basis of prevention of or concern for misuse.
 - i. Review at least every 2 years and have a process for adding and removing medications from the list.
 - ii. ISMP provides a list of high-alert medications as a starting point for evaluation.
 - b. Restrict access to high-alert medications by storing them in locked-lidded bins.
 - c. Restrict clinicians who order, prepare, and administer high-alert medications by requiring special education or credentialing to perform these tasks.
 - d. Implement equipment and supplies to support stronger mitigations such as designated color-coded epidural tubing, designated pumps for epidural infusions, or oral syringes that are unable to connect to parenteral tubing
 - e. Improve access to drug information and actionable decision support. Examples include linking to online drug information or policies and procedures from the electronic health record (EHR), or creating clinical alerts in automated dispensing cabinets or infusion pumps.
 - f. Use redundancies:
 - i. Independent double-check by two clinicians before medication administration
 - (a) Widely used as an error reduction strategy for high-alert medications, though no data show efficacy in reducing errors
 - (b) Challenges
 - (1) Requires judicious use not to overwhelm clinicians and devalue the usefulness
 - (2) Requires clinicians to perform checks independently
 - (3) Often used as the sole error mitigation strategy, even though it still relies on human checks
 - ii. Use both brand and generic names for certain medications such as insulin
 - iii. Technology such as barcoding for preparation, dispensing, and administration
 - iv. Require both the weight-based dose (such as mg/kg) and the calculated dose for pediatric patients
 - g. Provide mandatory patient education with information on types of errors and how to avoid them
 - h. Use Risk Evaluation and Mitigation Strategies (REMS), when available, for specific medications
 - i. Require the use of corollary orders, order sets, and other clinical decision support when prescribing to improve standardization, monitoring for safety, and availability of rescue medications

4. Easily confused drug names (look-alike sound-alike medications) error reduction strategies
 - a. Identify medications that may easily be confused: ISMP and FDA provide lists as starting points.
 - b. Use tall man lettering.
 - c. Limit use of verbal orders and require repeat back if used.
 - d. Use both brand and generic names or only generic names, depending on the risk factor for the error.
 - e. Require indication of use in the order.
 - f. Limit abbreviations.
 - g. Purchase products from different manufacturers and/or purchase different container sizes to minimize look-alike confusion.
 - h. Store in separate or secure locations or use technology for dispensing.
5. Technology
 - a. Electronic health record
 - i. HealthIT.gov defines an EHR as a digital version of a patient's paper chart. EHRs are real-time, patient-centered records that make information available instantly and securely to authorized users.
 - ii. Allows a broad view of patient information to be accessible anywhere and can therefore improve access to information by all members of the clinical care team
 - b. Computer provider/physician order entry (CPOE)
 - i. CPOE is an order entry application designed to help create and manage medical orders.
 - ii. Several studies of pediatric patients have shown a decrease in both prescribing errors and ADEs.
 - iii. Potential benefits
 - (a) Can eliminate transcription errors when orders are entered directly by the ordering provider
 - (b) Can improve the timeliness of order processing
 - (c) Allows for forcing functions in design to minimize errors and omissions of critical information such as:
 - (1) Patient weight documentation before order placement
 - (2) Allergy documentation before order placement
 - (3) Unit of measure restrictions
 - (4) Route of administration restrictions
 - (5) Indication documentation within the medication order
 - (d) May be paired with clinical decision support to strengthen error mitigation strategies
 - iv. Pediatric considerations
 - (a) Customization is required because most vendors do not support pediatric content.
 - (b) A patient's metric weight (in kilograms) should be required for all orders.
 - c. Clinical decision support (CDS)
 - i. CDS is a process to enhance decision and actions by health care providers and patients, using organized clinical knowledge and person-specific information, intelligently filtered and presented at appropriate times, to enhance and improve health and health delivery.
 - ii. CDS tools include:
 - (a) Dose alerts
 - (b) Order sets
 - (c) Drug-drug interaction checking
 - (d) Allergy interaction checking
 - (e) Duplicate order checking
 - (f) Clinical guidelines
 - (g) Documentation templates
 - (h) Diagnostic support

- iii. Pediatric considerations
 - (a) Dose range checking should address weight-based dosing as well as adult maximum dosing.
 - (b) Dose-checking parameters often require customization because vendors do not support pediatric content.
- d. Electronic prescribing (e-prescribing)
 - i. Electronic transmission of prescriptions or prescription-related information between a prescriber, dispenser, pharmacy benefits manager, or health plan. Computer to computer, does not include use of email or fax
 - ii. e-Prescribing functions and benefits
 - (a) Electronically transmits prescriptions, reducing transcription errors, improving timeliness, decreasing telephone calls, and improving patient convenience
 - (b) Generates messages regarding new prescriptions, prescription changes, and refill requests, improving the timeliness of prescription processing
 - (c) Prescription fill status notification and prescription cancellation
 - (d) Medication history information availability, improving ability to perform medication reconciliation and assess patient adherence
 - (e) Integrates CDS for safety checks, reducing errors in dosing and contraindications
 - (f) Provides information on cost, therapeutic alternatives, and formulary, improving patient adherence
 - (g) Allows for electronic prior authorization requests, improving timeliness for patients
 - (h) Education abilities for patients and provider feedback
- e. Pharmacy information systems (PIS)
 - i. The PIS is either a stand-alone information system or a subsystem of the hospital information system that supports the pharmacy staff's management of the medication use system.
 - ii. May have a unidirectional interface, bidirectional interface, or no interface or may be fully integrated with the EHR
 - iii. PIS functions and safety benefits:
 - (a) Contains patient demographics and allergy information
 - (b) Has pharmacy-focused CDS
 - (c) Allows for clinical pharmacist verification of orders
 - (d) Manages pharmacy supply chain for medication dispensing
 - (e) Provides ability to maintain medication history information
 - (f) Manages medication inventory processes
 - (g) Supports barcode processes for medication preparation and dispensing
 - (h) Supports medication compounding software and processes
- f. Risks with CPOE, e-prescribing, CDS, and PIS:
 - i. Reliance on technology
 - ii. Minimal vendor-supplied dose rules for pediatric patients
 - iii. Alert fatigue
 - iv. Product selection errors
 - v. Miss-selections from dropdown menus
 - vi. Downtime
 - vii. Blind acceptance of defaults
 - viii. Character limits
 - ix. Medication tapers, titrations, and uneven dosing limitations
 - x. Cost of implementation and maintenance

- g. Electronic medication administration record (e-MAR)
 - i. Software that allows for electronic tracking of medication orders for administration and administration information and documentation
 - ii. May be stand-alone or may interface with the EHR
 - iii. Benefits of an e-MAR
 - (a) Decreases medication errors
 - (b) Supports CDS for clinicians administering medications
 - (c) Improves the timeliness of medication order transmittal to the administering clinician
 - (d) Improves the accuracy and timeliness of medication administration documentation
 - (e) Supports the implementation of barcode medication administration (BCMA)
- h. BCMA
 - i. BCMA is a technology that reads barcodes on the patient identification (ID) band and medications to match the patient and medication to prevent medication errors at the point of medication administration.
 - ii. Several studies of adults have shown 27.3%–87% reductions in medication errors.
 - iii. One study of a neonatal ICU showed a 47% reduction in preventable ADEs.
 - iv. Medication barcodes scanned may be those from the manufacturer, those created by a secondary pharmacy barcode management system, or the PIS.
 - (a) Barcodes supplied by the manufacturer contain information to identify the drug product, such as the National Drug Code (NDC).
 - (b) Barcodes generated from a secondary barcode management system may contain information to identify the drug product, such as the NDC.
 - (c) Barcodes generated by the PIS may contain the order number specific for a patient but not information to identify the drug product, such as the NDC.
 - v. BCMA is intended to provide a double-check on the “5 rights” of medication administration; however, it cannot check them all.
 - (a) Right patient
 - (1) The patient ID band barcode references the patient’s medical record, and the medication barcode matches to an order in the patient’s medical record. Together, this verifies that the medication is for that patient.
 - (2) For products that come in bulk packages such as inhalers, the patient may have an order for the medication, but the actual inhaler may be labeled for another patient. When using the NDC barcode, this error cannot be detected by BCMA.
 - (b) Right drug
 - (1) When barcodes containing the NDC are used, the drug product can be matched to the NDC in the medication order in the patient’s medical record to verify the correct drug product was selected.
 - (2) When barcodes do not contain the NDC information but only an order ID, BCMA cannot verify whether the correct drug product was selected. This is often true in pediatric patients when oral liquid or parenteral products are prepared in patient-specific unit doses.
 - (c) Right dose (prescribed and prepared)
 - (1) When the barcode contains the NDC of a medication and the NDC is specific for the dose on the package, such as a 2-mg tablet versus a 4-mg tablet, the dose of the product can be verified against the patient’s prescribed order.
 - (2) For medications prepared in syringes, intravenous bags, or other non-manufacturer-supplied containers, the prepared dose (e.g., volume of medication in syringe) cannot be verified by BCMA.

- (d) Right route
 - (1) When the barcode contains the NDC of the medication, the dosage form can be verified against the patient's medication order.
 - (2) BCMA cannot verify the route through which the medication is actually administered to the patient. Thus, for example, BCMA cannot prevent an intravenous medication from being administered orally by the administering clinician.
 - (e) Right time
 - (1) When the patient ID band and medication barcodes are scanned, the BCMA system can verify the time the medication is due to verify the right time for administration.
 - (2) There are gaps in the ability of BCMA to verify the right time for as-needed medications.
 - (f) Right indication and contraindication
 - (1) BCMA cannot verify the right indication for the medication.
 - (2) BCMA may include CDS parameters to alert the administering clinician of contraindications such as allergies, drug-drug interactions, and dose concerns.
- vi. Many workarounds and risks exist with the use of BCMA.
 - (a) Reluctance to wake sleeping or swaddled children can produce workarounds with patient identification.
 - (b) ID band not on patient; especially in pediatric and neonatal patients when there is concern for skin integrity, children may not tolerate wearing the ID band, and children may play with the ID band and remove it like a bracelet
 - (c) Computer screen out of visual field
 - (d) Visual matching and checks omitted
 - (e) Medication barcode not on medication when scanned
 - (f) Scanning one package when several packages are used
 - (g) Scanning after administration
 - (h) Documentation of administration completed before ingestion by patient
 - (i) Not stopping to resolve an alert
 - (j) Torn or poorly placed labels
 - (k) Configuration and location of the scanner and screen
 - (l) Patients under isolation affecting use of technology in the patient's room
 - (m) Impact of other barcode systems such as those for breast milk, point-of-care laboratory testing, laboratory specimen collection
- i. Smart pump infusion technology
 - i. A "smart" pump is an infusion pump that contains dose error reduction software (DERS). DERS is also called "drug libraries" because it results in a list of medications with dosing guidelines, limits, and alerts for selection when the pump is programmed.
 - ii. One study of pediatric patients showed that smart pump technology in conjunction with standard concentrations and medication labels decreased reported medication errors by 73%.
 - iii. Drug libraries design
 - (a) Drug names should match the MAR to facilitate verification by the clinician administering the medication.
 - (b) Pediatric medications often use more than one concentration. This results in either several entries for the same medication or manual entry of the concentration.
 - (1) Both pose safety risks and should be considered carefully in the design.
 - (2) Use of standard concentrations can facilitate library use and provide an additional safety feature.
 - (c) Infusion rate limits are affected by indication, drug concentration, central versus peripheral administration, availability of monitoring, and institutional and individual nursing practice.

- (d) Dosing limits
 - (1) Soft-stop dose limits can be overridden by the administering clinician.
 - (2) Hard-stop dose limits cannot be bypassed by the administering clinician.
 - (3) Development of a pediatric-specific library should account for dose limit alerting across all pediatric age and weight ranges.
- (e) Drug libraries can help restrict the availability of dosing units. In pediatric patients, many dosing units are used for intravenous infusions, increasing the risk of a medication error. Dosing units commonly used in pediatric patients: mL/hr, mcg/hr, units/hr, mg/hr, mcg/kg/hr, units/min, mg/kg/hr, mcg/kg/min, units/kg/hr.
- (f) Care area profiles allow for limiting medications and dosing parameters in the library to unique patient populations.
- (g) Clinical advisories can be used to convey important information about specific medications, such as high-alert status, at the time of pump programming.
- iv. Continuous quality improvement data can be used to evaluate medication administration practices for risk points and great catches.
- v. Smart pumps: Interoperability with the EHR
 - (a) When interoperability is bidirectional, the medication information is sent from the EHR to the pump according to the medication order.
 - (b) Interoperability decreases the need for manual programming of the pump.
- j. Technology for preparation and dispensing activities
 - i. Literature evaluating the impact on medication errors and ADEs of these technologies is sparse. However, many of the technologies have become widespread for reasons other than safety but are believed to help decrease the risk of medication errors.
 - ii. Pharmacy dispensing technology
 - (a) Helps minimize mispicking errors with look-alike sound-alike medications
 - (b) Barcode technology helps ensure correct medication is loaded and dispensed.
 - (c) Carousel dispensing systems and robotic picking systems
 - (1) Computerized drug storage devices within the pharmacy
 - (2) Barcode scanning for stocking. Risk: Often, only one package is scanned when several packages are stocked.
 - (3) One study showed a decrease in medication picking errors.
 - (d) Automated dispensing cabinets
 - (1) Computerized drug storage device intended for patient care areas
 - (2) Barcode scanning for restocking may prevent mix up errors; however, often only one package is scanned when several may be stocked.
 - (3) Medications can be placed in lidded or locked-lidded bins to drive the user to the correct bin on the basis of the medication selected and avoid mispicking errors.
 - (4) Restrictions can be implemented to prevent removal of medications if an order is not placed in the EHR for the patient.
 - (5) Limitations on patient-specific ready-to-administer doses in pediatric patients. Stocking of several sizes of the same medication is necessary to minimize drug manipulation in the patient care areas.
 - (6) There is a risk of stocking medications when the dosage form is used off-label, which occurs in pediatric patients. For example, intravenous midazolam used for intranasal dosing could be administered by the incorrect route when stocked, dispensed, and prepared in the patient care area.

- iii. Automated compounding, intravenous workflow systems, and repackaging technology
 - (a) These technologies can improve the safety of high-risk intravenous compounding for both patients and staff.
 - (b) Intended to improve the accuracy of intravenous medication preparation
 - (c) Intravenous robotics technology
 - (1) Prepare intravenous medication doses, including chemotherapy
 - (2) Accuracy measures may be exceeded.
 - (3) Data do not support a decrease in medication errors affecting patient harm.
 - (d) Compounding pumps
 - (1) Used for making complex parenteral preparations such as parenteral nutrition
 - (2) Can interface with the PIS to minimize programming errors
 - (e) Unit dose repackagers
 - (1) Package bulk medication in unit dose packages.
 - (2) Barcode technology helps ensure correct medication is loaded for repackaging.
 - (3) These machines can also place barcodes on the unit dose package required for BCMA.
 - (4) Some machines can halve and quarter tablets as required to obtain unit dose packages for pediatric patients.
6. Other medication use system design strategies for error reduction:
 - a. Use scales that weigh only in metric units of kilograms or grams in the neonatal ICU and consider using scales that interface with the EHR to minimize transcription errors.
 - b. Strong formulary management programs:
 - i. Limit the medications available
 - ii. Improve the ability to be familiar with dosing, preparation, and administration requirements
 - iii. Limit the number of medications required to be in the EHR
 - c. Drug shortage program that includes system evaluation for risks and errors, impact on existing error prevention strategies, and implementation of mitigation strategies before use of the replacement product
 - d. Minimize the use of verbal orders and repeat back all order elements when verbal orders are necessary
 - e. Avoid the use of abbreviations throughout the medication use system to support clear communication, avoid misreading, and avoid confusion about meaning
 - f. A pharmacist should review all orders for appropriateness before preparing and dispensing medications, except in emergencies.
 - g. Dispense medications in unit-of-use, ready-to-administer form. In pediatric patients, many medications will need to be custom prepared in patient-specific unit doses.
 - h. Require a pharmacist's visual verification of all product preparation before further manipulation or final mixing of sterile products
 - i. Do not use the "pull-back method" to verify syringe volume.
 - ii. If using technology to capture drug preparation, pharmacist verification should occur before the product is dispensed to the patient care area.
 - i. Use syringe, tubing, and connection device distinctions to prevent wrong route errors: Oral, intravenous, epidural, or intrathecal on the basis of intended use, especially when medications are being used for a different route than originally intended. Use products that comply with the ISO tubing connector standards as a forcing function.
 - j. Consider standardized doses to minimize the number of unique patient doses prepared.
 - k. Use commercially available products, when possible.

- l. Limit compounding and manipulation of medication products to the pharmacy staff, when possible.
 - m. Provide readily available resources on the appropriateness of crushing medications.
 - n. Limit and standardize concentrations to reduce the need for calculations, minimize inventory, and decrease selection options in various technologies.
 - i. When more than one concentration is needed, which is common in pediatric patients, have standard concentration descriptions and displays on all labels.
 - ii. Ensure all concentrations are available for ordering in the CPOE and PIS.
 - iii. National standards are available on the Standardize 4 Safety website for both oral liquid compounds and continuous infusion medications: <https://www.ashp.org/Pharmacy-Practice/Standardize-4-Safety-Initiative#national>
 - o. Design workspaces and processes to minimize distractions.
 - p. Evaluate and improve the use of patient names for confirming the right patient.
 - i. Newborns are especially prone to patient name errors because they often do not have a unique first name immediately after birth.
 - ii. Newborn patients can be difficult to distinguish from each other.
 - iii. Twins will have the same date of birth, last name, parent name, often the same sex, and sequential medical record numbers.
 - q. Standardize medication label designs to align with the intended user's processes for medication checking. Separate the administration (or nursing) label from the pharmacy preparation label.
 - r. Evaluate and establish medication reconciliation processes at all transitions of care. In pediatric patients, this will need to include a knowledgeable caregiver for the patient.
7. Education
- a. Although education is a low-leverage change strategy, it is necessary for safety.
 - b. Educational interventions should be paired with additional, stronger mitigation strategies.
 - c. All staff involved in the medication use system should be educated on causes and risks of errors in their work processes and the strategies used to mitigate them.
 - d. Patients should be educated on medication dosing, adverse effects, purpose and effectiveness, and common errors and how to avoid them.
 - i. Use repeat back to assess the patient's understanding of medication information.
 - ii. Ensure that verbal and written documentation align with health literacy standards.
 - iii. Encourage the use of patient portals for ready access to health care information.
 - iv. Listen and address concerns from the patient or family; they may be detecting an error.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES**1. Answer: D**

This event is both an ADE and an ADR according to the American Society of Health-System Pharmacists and World Health Organization definitions, making Answer D correct and Answers B and C incorrect. This is not a near miss because the event reached the patient, making Answer A incorrect.

2. Answer: C

This event would be classified as a category E event because it reached the patient and required an intervention to treat temporary harm (Answer C is correct). Answers A and B are incorrect because categories A and B are for events that do not reach the patient. Answer D is incorrect because category I is for events resulting in patient death.

3. Answer: B

It is also recommended to use medications with manufacturer-produced dosage forms when clinically appropriate (Answer B is correct). Answer A is incorrect because the use of primary literature-based extemporaneously compounded formulations should occur only when there is no therapeutic alternative using a commercially available product. Answers C and D are incorrect because the use of non-evidence-based formulations should be prohibited.

4. Answer: C

Forcing functions including hard stops is the most effective risk reduction strategy, making Answer C correct. Education and policy development, although necessary, are less effective strategies; therefore, Answers A, B, and D are incorrect.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: C**

The NCC MERP organization provides the standard scoring and classification system for medication safety events (Answer C is correct; Answers A, B, and D are incorrect).

2. Answer: C

Barcode medication administration, smart pump technology, and computerized have all been shown to decrease medication errors, making Answers A, B, and D incorrect. There is no primary literature supporting that the two-clinician independent double-check decreases medication errors, making Answer C correct.

3. Answer: D

According to the ISMP's rank order of error reduction strategies, forcing functions, such as requiring a monitoring value to be used for calculating doses, have the greatest potential to reduce medication errors, making Answer D correct and Answers A–C incorrect.

4. Answer: D

Using trigger tools to detect patient harm has been shown in the literature to capture almost 10 times as many patient safety events as voluntary reporting, making Answer D correct and Answers A–C incorrect.

5. Answer: A

This patient is taking ciprofloxacin for an off-label indication. Fluoroquinolones are not FDA approved for neonates, making Answer A correct. All other described scenarios include FDA-approved indications and dosage forms, making Answers B–D incorrect. The risk of a medication safety event increases with off-label indications and nonstandard dosage forms.

6. Answer: C

Captopril is not available in a commercially available liquid formulation; however, all the other answer selections are available in this formulation, making Answer C correct and Answers A, B, and D incorrect. Using extemporaneously compounded liquid formulations and/or nonstandard formulations presents a risk factor for medication errors.

7. Answer: B

The need for manipulating manufacturer-provided dosage forms reduces the ability to use the National Drug Code number as a medication identifier. This reduces the ability to confirm the product and dose when barcode scanning is used at the bedside, making Answer B correct. All the other answers are challenging when using barcoding but are not pediatric-specific, making Answers A, C, and D incorrect.

8. Answer: B

Off-label medications may have limited information regarding the pharmacokinetic parameters at differing developmental stages of pediatric patients, given the limited or lack of studies conducted regarding pharmacokinetic parameters in the pediatric patient population. According to the American Academy of Pediatrics policy statement on use of off-label drugs in children, use is not improper, illegal, contraindicated, or investigational and does not require special consent if not being used experimentally. In addition, use is supported by evidence. Use of off-label drugs is intended to benefit the individual patient, as determined by the provider's medical judgment that it is the best medical treatment for the patient. Use of off-label medications in pediatric patients is common, and although ADEs may be unknown, this is not a reason to avoid use but instead to monitor for ADEs and report them when they occur. Publications regarding clinical experience, guidelines for use, handbooks, consensus statements, policy statements, and peer-reviewed literature on the use of off-label medications in children are often available, even if the medication has not been used to add indications for use to the manufacturer's labeling, making Answer B correct and Answers A, C, and D incorrect.

9. Answer: A

Given the difference in the voluntary reporting infrastructure such as reporting systems, degree of nonpunitive response to error, staff psychological safety, and hospital error detection methods, it is not possible to compare medication safety error rates across several organizations, making Answer A correct and Answers B–D incorrect. This statement is endorsed and supported by NCC MERP and ISMP.

10. Answer: B

An organization's punitive response to patient safety events has commonly been cited as challenging the staff's comfort with event reporting. Building a nonpunitive culture is vital to ultimately improving this reporting, making Answer B correct. All the other statements are inaccurate, making Answers A, C, and D incorrect.

PICU I

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**XAVIER UNIVERSITY OF LOUISIANA COLLEGE OF PHARMACY/
LOUISIANA STATE UNIVERSITY HEALTH SCIENCES
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NEW ORLEANS, LOUISIANA**

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Learning Objectives

1. Develop an appropriate treatment plan for patients with sepsis.
2. Recommend appropriate treatment strategies to manage sedation, delirium, and withdrawal prevention strategies in critical care patients.
3. Based on pharmacokinetic changes that occur during extracorporeal membrane oxygenation (ECMO), optimize patient's medication therapy while deployed on ECMO.
4. Differentiate between various therapeutic options for cardiac arrest and when to use each therapy and algorithm.
5. Compare and contrast various modalities for the optimization of mean arterial and intracranial pressure in traumatic brain injury (TBI).
6. Devise a fluid replacement and secondary response prevention plan for patients with severe burns.

Abbreviations

AV	Atrioventricular
CPP	Cerebral perfusion pressure
CPR	Cardiopulmonary resuscitation
ECMO	Extracorporeal membrane oxygenation
ET	Endotracheal
ICP	Intracranial pressure
ICU	Intensive care unit
MAP	Mean arterial pressure
PALS	Pediatric advanced life support
PEA	Pulseless electrical activity
PICU	Pediatric intensive care unit
SIRS	Systemic inflammatory response syndrome
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
TBI	Traumatic brain injury
TBSA	Total body surface area
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Self-Assessment Questions

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

1. A 5-year-old boy presents in septic shock with a temperature of 102.5°F (39.2°C). His blood pressure is 60/40 mm Hg, his heart rate is 100 beats/minute, and he is cool to the touch. Which is the most appropriate vasopressor to initiate first?
 - A. Dopamine.
 - B. Vasopressin.
 - C. Milrinone.
 - D. Epinephrine.
2. An 8-year-old boy (weight 30 kg) sustained burns to 40% of his body after accidentally pulling boiling water off the stove. Which is the most appropriate way to replace his fluids?
 - A. 300 mL/hour for 24 hours.
 - B. 450 mL/hour for 8 hours; then 225 mL/hour for 16 hours.
 - C. 225 mL/hour for 8 hours; then 450 mL/hour for 16 hours.
 - D. 225 mL/hour for 8 hours; then 112 mL/hour for 16 hours.
3. A 7-year-old patient is currently on a fentanyl infusion at 1 mcg/kg/hour and is in the process of being deployed on extracorporeal membrane oxygenation (ECMO). Which best describes the pharmacokinetic change that is expected to occur with fentanyl while the patient is on ECMO?
 - A. Decreased volume of distribution.
 - B. Adsorption to the circuit.
 - C. Increased clearance.
 - D. No changes to fentanyl pharmacokinetics.
4. A 4-month-old child with no significant past medical history presents with respiratory failure secondary to respiratory syncytial virus. Mechanical ventilation has been maximized, with little improvement in the patient's clinical status. The decision is made to start ECMO. Which is the most appropriate anticoagulant to use during ECMO?
 - A. Heparin.
 - B. Warfarin.
 - C. Enoxaparin.
 - D. Aspirin.
5. A 6-year-old girl presents in shock. She has a past medical history significant for a dilated viral cardiomyopathy with a baseline ejection fraction of 45%. Her current ejection fraction is 35%. Her current blood pressure is 130/80 mm Hg. Which is

- the most appropriate agent to use in this child for cardiac support?
- A. Norepinephrine.
 - B. Milrinone.
 - C. Dopamine.
 - D. Phenylephrine.
6. A 9-year-old mechanically ventilated child goes into cardiac arrest in the intensive care unit (ICU). Earlier that day, the child lost intravenous access, and the team is unable to obtain a new line. Which drug would be most appropriate to give endotracheally to this child?
- A. Calcium chloride.
 - B. Epinephrine.
 - C. Amiodarone.
 - D. Vasopressin.
7. A 3-year-old is in supraventricular tachycardia (SVT). Which is the most appropriate way to administer adenosine?
- A. Intravenous push over 2–5 minutes, followed by a saline flush over 2–5 minutes.
 - B. Diluted infusion over 30 minutes.
 - C. Rapid intravenous push, followed by a saline flush over 2–5 minutes.
 - D. Rapid intravenous push, followed by a rapid saline flush.
8. Cardiac arrest is called on a 4-year-old girl on the floor. The team begins cardiopulmonary resuscitation (CPR), and the monitor reveals ventricular fibrillation (VF). The team does three cycles of CPR, defibrillation, and epinephrine with no return to spontaneous circulation. Which drug would be best to consider next?
- A. Atropine.
 - B. Adenosine.
 - C. Amiodarone.
 - D. Procainamide.
9. E.G. is a 3-year-old girl who presents to the emergency department with lethargy, increased respiratory rate, hypotension, weak pulses, and poor capillary refill. Her heart rate is 200 beats/minute. Her medical history is significant for tuberous sclerosis with a large rhabdomyoma on the left ventricular septum. An electrocardiogram (ECG) shows monomorphic wide QRS complexes (greater than 0.09 seconds) with absent P waves. Which would be best for treating E.G.?
- A. Amiodarone.
 - B. Synchronized cardioversion.
 - C. Lidocaine.
 - D. Magnesium.
10. After initial intervention, E.G.'s ECG now shows wide, polymorphic QRS complexes with a QRS axis shifting back and forth around the isoelectric baseline (i.e., torsades de pointes). Which would be best for treating E.G.?
- A. Amiodarone.
 - B. Synchronized cardioversion.
 - C. Lidocaine.
 - D. Magnesium.
11. A 3-year-old involved in a motor vehicle collision sustained a severe traumatic brain injury (TBI). Mannitol is used to help control the patient's intracranial pressure (ICP). Which best matches the mechanism of action of ICP reduction with mannitol's duration or onset?
- A. Blood viscosity reduction lasts 6 hours.
 - B. Blood viscosity reduction lasts 1 hour.
 - C. Osmolar agent starts working within 2 minutes.
 - D. Osmolar agent lasts 1 hour.
12. A 5-kg patient is receiving adequate sedation with fentanyl and midazolam, scheduled mannitol 5 g every 6 hours, and 3% saline continuous infusion at 5 mL/hour for ICP management. Osmolarity is 350 mOsm/L, and serum sodium is 175 mEq/L. Which is the next most appropriate agent for management of an increased ICP?
- A. A 7-mL/kg bolus of 3% saline.
 - B. Mannitol 0.5 g/kg x 1 now (regardless of timing of previous mannitol).
 - C. Pentobarbital bolus, followed by continuous infusion.
 - D. Phenytoin every 8–12 hours.

13. A 2-year-old is 5 days post-severe scald injury burn to 45% of her body. Which most accurately describes how propranolol would help?
- A. Increase heart rate.
 - B. Increase resting energy expenditure.
 - C. Decrease resting energy expenditure.
 - D. Decrease lean body mass.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5, 1.6
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.1, 2.2, 2.4
3. Domain 3: Information Management, Research, and Education; Task(s): 3.1
4. Domain 4: Public Health and Patient Advocacy; Task(s): 4.1, 4.3

I. SHOCK**A. Types of Shock**

1. Hypovolemic
 - a. Dehydration, hemorrhage
 - b. Tachycardia, sodium and water retention through the renin angiotensin aldosterone system, anti-diuretic hormone
 - c. Covered in the “Fluids, Electrolytes, and Nutrition” chapter.
2. Cardiogenic shock
 - a. Acid-base imbalance, severe electrolyte disorders, poor myocardial function, heart failure, etc.
 - b. Usually fluid overload states (see the “Cardiology” chapter)
3. Distributive shock: Septic, anaphylactic, neurogenic, spinal
4. Obstructive shock: Tamponade, aortic stenosis, etc.

B. Septic Shock: Definitions

1. Systemic response to infection
2. Mortality rate 2%–10%
3. Decreased perfusion to tissues
4. Spectrum of severity: See Figure 1.
 - a. Systemic inflammatory response syndrome (SIRS)
 - b. Sepsis
 - c. Sepsis-associated organ dysfunction (severe sepsis)
 - d. Septic shock
5. Cardiovascular dysfunction:
 - a. Hypotension or need for vasopressor
OR
 - b. Two of the following: Metabolic acidosis, $\uparrow$ lactate, $\downarrow$ urine output, $\uparrow$ capillary refill time, gap in core to peripheral temperature
 - c. Children can maintain blood pressure longer than can adults; if hypotensive, then decompensated shock
6. Respiratory dysfunction (just one criterion must be met):
 - a. $\downarrow$ PaO_2 /fraction of inspired oxygen (FiO_2) ratio (less than 300)
 - b. $\uparrow$ PaCO_2
 - c. FiO_2 greater than 50%
 - d. Mechanical ventilation
7. Must meet two criteria of the organ systems below (a–d) for severe sepsis:
 - a. Neurologic: Glasgow Coma Scale score of 11 or less or a change of 3 points with a mental status change
 - b. Hematologic:
 - i. Platelet count less than 80,000/mm³ or a 50% drop
OR
 - ii. INR (international normalized ratio) greater than 2
 - c. Renal: Serum creatinine (SCr) 2 x normal (or $\uparrow$ from baseline)
 - d. Hepatic: Total bilirubin 4 mg/dL or greater or ALT (alanine aminotransferase) 2 x normal

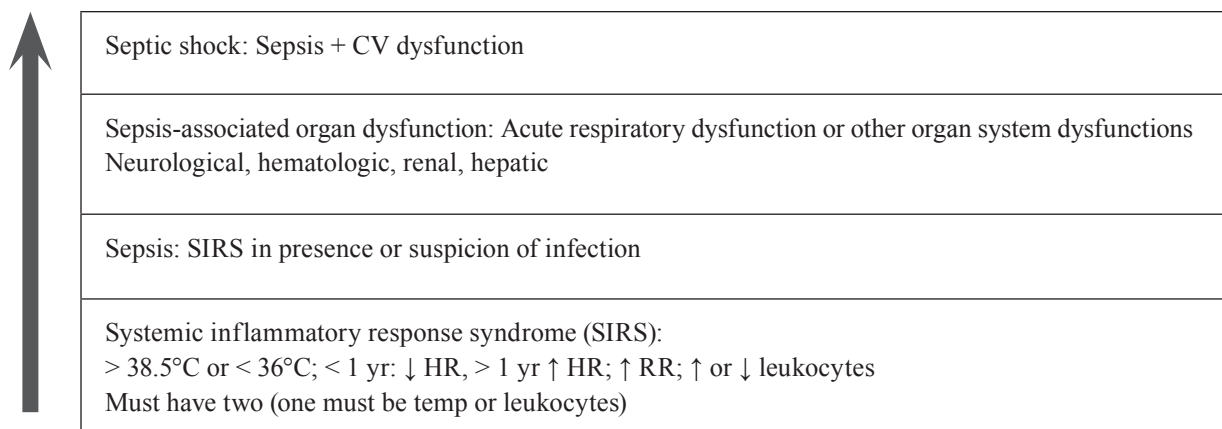


Figure 1. Sepsis spectrum of severity.

CV = cardiovascular; HR = heart rate; RR = respiratory rate.

C. Risk Factors

1. Indwelling catheters
2. Immune system dysfunctions (oncology, HIV, asplenia, malnutrition, etc.)
3. Urinary tract infections
4. Pneumonia
5. Age (neonates at higher risk)
6. Chronic medical issues (lung disease, congenital heart disease, neuromuscular disease)
7. Sickle cell disease

D. Pathophysiology

1. Activation of cytokines → vasodilation, increased capillary permeability, and cardiovascular dysfunction
2. Proinflammatory cytokine release: Tumor necrosis factor alpha (TNFα), interleukin (IL-1, IL-6, and IL-8) platelet-activating factor, nitric oxide released, and high concentrations implicated in disseminated intravascular coagulopathy
3. Endotoxins change the endothelium, making it more procoagulant, producing microthrombi

E. Treatment

1. Oxygen through noninvasive means first; then mechanical ventilation if respiratory failure
2. Access
 - a. Intravenous (central or peripheral)
 - b. Intraosseous
3. Fluid resuscitation:
 - a. Examples of goals used:
 - i. Capillary refill of 2 seconds or less
 - ii. Normal blood pressure (can give fluid even if not hypotensive because once hypotensive, cardiovascular collapse usually occurs)
 - iii. Urine output greater than 1 mL/kg/hour
 - iv. Normal mental status
 - v. Normal pulses (central and peripheral the same)
 - vi. ScvO₂ (central venous oxygen saturation) of 70% or greater
 - b. Administration
 - i. Settings with intensive care services: 10- to 20-mL/kg fluid bolus (40–60 mL/kg total)
 - ii. Settings without intensive care services: 10- to 20-mL/kg fluid bolus up to 40 mL/kg

- iii. Balanced/buffered crystalloid solutions (lactated Ringer solution or balanced salt solution) are preferred over 0.9% saline.
- 4. Antibiotics:
 - a. Broad spectrum
 - i. Within first hour of recognition of shock
 - ii. Within 3 hours if not shock
 - iii. Empiric therapy should be determined on the basis of risk factors, baseline immune system function, and history of multidrug-resistant organisms.
 - b. Blood cultures before administration
 - c. Use clindamycin if toxic shock
- 5. Vasopressor support (see Table 1)
 - a. Use early in treatment to support blood pressure.
 - b. Agents:
 - i. Epinephrine or norepinephrine first line
 - ii. Dopamine no longer first line
 - iii. May modify agents on the basis of advanced hemodynamic monitoring
 - (a) Milrinone or dobutamine in low cardiac output high systemic vascular resistance (SVR) states
 - (b) Can use dopamine if norepinephrine or epinephrine not available
 - (c) Clinical parameters of “cold vs. warm” shock are not focus of agent choice, but may be used in conjunction
 - c. If SVR is still low, can consider vasopressin
- 6. Corticosteroids:
 - a. May be used for catecholamine-refractory shock
 - b. Hydrocortisone 50 mg/m²/day (up to 100 mg/m²/day) divided every 6 hours (alternative dosing: 0.5–2 mg/kg/dose every 6 hours)
- 7. Glucose control:
 - a. 180 mg/dL or less
 - b. Avoid hypoglycemia.
 - c. Tight glucose control not usually done in the pediatric intensive care unit (PICU)
- 8. Medication safety:
 - a. Units of drips
 - b. Proper dosing of antibiotics
 - c. Prompt administration of the antibiotics: Entire medication use system

Table 1. Vasopressor and Inotropes in Shock

Agent	Receptor(s)/MOA	Continuous Infusion Dose	Clinical Effects	Notes
Dopamine	Dopamine, + β 1 + α 1 +++ β 1 ++ α 1, +++ β 1	1–5 mcg/kg/min 5–9 mcg/kg/min 10–20 mcg/kg/min	Not significant Increased SVR + cardiac index Increased SVR and cardiac index	Usually dosed 5–10 mcg/kg/min in sepsis
Epinephrine	++ α 1, +++ β 1 +++ α 1, ++ β 1	0.01–0.05 mcg/kg/min 0.05–0.3 mcg/kg/min	Increased SVR and contractility	Increases glucose and lactate
Norepinephrine	+++ α 1, + β 1, + β 2	0.05–2 mcg/kg/min	Increased MAP and SVR with little cardiac effect	More potent than dopamine (alpha effects)

Table 1. Vasopressor and Inotropes in Shock (*continued*)

Agent	Receptor(s)/MOA	Continuous Infusion Dose	Clinical Effects	Notes
Dobutamine	+ α_1 , ++ β_1 +++ α_1 and +++ β_1	2–10 mcg/kg/min 10–20 mcg/kg/min	Increased contractility and SVR	Children younger than 12 months usually less responsive
Milrinone	Type 3 phosphodiesterase inhibitor	0.25–0.75 mcg/kg/min Higher doses used clinically	Increased cAMP contractility	Hypotension Renally cleared
Vasopressin	V1 receptor	0.17–8 milliunits/kg/min	Increased SVR	Watch dosing and units for errors
Phenylephrine	α_1	0.1–0.5 mcg/kg/min	Increased SVR, no cardiac effect	

cAMP = cyclic adenosine monophosphate; MAP = mean arterial pressure; min = minute(s); MOA = mechanism of action; SVR = systemic vascular resistance.

Patient Case

Questions 1–3 pertain to the following case.

A 5-year-old patient with no significant medical history presents to the emergency department in January with tachycardia (120 beats/minute), a temperature of 102°F (39°C), and an elevated white blood cell count of 25×10^3 cells/mm³. Both the basic metabolic panel and the liver function tests are normal.

- Which best describes the patient's stage of sepsis?
 - SIRS.
 - Sepsis.
 - Sepsis-associated organ dysfunction.
 - Septic shock.
- While the team is examining the patient, a nurse notices a warm red area around the child's ankle. On questioning, the mother explains that he was cut in that area 5 days ago and that it did not heal correctly. A blood pressure reading is taken, which is 60/40 mm Hg. Which best represents the patient's stage of sepsis now?
 - SIRS.
 - Sepsis.
 - Sepsis-associated organ dysfunction.
 - Septic shock.
- The team initiates two rounds of lactated Ringer solution 20 mL/kg and is almost ready to initiate the third when the medical resident hears rales in the lungs. The patient's blood pressure is 65/45 mm Hg, and he has cold extremities. Which is the next most appropriate step for this patient?
 - Initiate dobutamine at 9 mcg/kg/minute.
 - Initiate milrinone at 0.5 mcg/kg/minute.
 - Initiate norepinephrine at 0.1 mcg/kg/minute.
 - Initiate lactated Ringer solution 10 mL/kg.

II. SEDATION/ANALGESIA/NEUROMUSCULAR BLOCKADE/INTENSIVE CARE UNIT DELIRIUM

A. Introduction

1. Many factors for pain and anxiety in the intensive care unit (ICU)
2. Separation from parents, sleep/wake disturbances, painful procedures
3. Indications: Endotracheal (ET) tubes, mechanical ventilation: reduce oxygen consumption, induce sleep, prevent self-extubation
4. Extreme variations in practice from site to site and practitioner to practitioner
5. Various scales can be used to assess (Comfort-B score, etc.)
6. Duration can be short for procedures or long (e.g., prolonged intubation or ECMO)
7. Uses a combination of anxiolytics and opioids (usually midazolam and fentanyl)

B. General Strategies: Anxiety

1. Anxiety has many causes; is generally treated with benzodiazepines
2. Midazolam and lorazepam used most often (see Table 2)
 - a. No analgesia
 - b. Causes amnesia
 - c. Lipophilic and metabolized in the liver
 - d. Midazolam has active metabolite that is renally eliminated
 - e. Can use a continuous infusion with bolus dosing as needed every 1–4 hours; bolus dose should equal at least 1 hour of continuous infusion. Intermittent scheduled (every 4–6 hours) lorazepam can be used as an option to drip because of its half-life.

Table 2. Benzodiazepines

Agent	Continuous Infusion Starting Dose	Bolus Dose	Onset (min)	Duration	Notes
Midazolam	0.05–0.1 mg/kg/hr or 0.5–1 mcg/kg/min	0.1 mg/kg	1–5	30 min	Use preservative-free product in neonates; active metabolite is renally eliminated
Lorazepam	0.03–0.1 mg/kg/hr	0.05–0.1 mg/kg	15–30	6–8 hr	Contains propylene and polyethylene glycol causing anionic gap metabolic acidosis

C. General Strategies: Pain

1. Many painful insults in PICU (ET tubes, procedures, etc.)
2. Opioids cause sedation.
 - a. No amnesia
 - b. Most commonly used includes morphine and fentanyl (see Table 3)
 - c. Use continuous infusion with bolus dosing as needed every 1–4 hours; bolus dose should equal at least 1 hour of continuous infusion.

Table 3. Opioids

Agent	Continuous Infusion Starting Dose	Bolus Dose	Onset (min)	Duration (hr)	Notes
Fentanyl	1 mcg/kg/hr	0.5–1 mcg/kg	1	0.5–1	Chest wall rigidity
Morphine	0.05 mg/kg/hr	0.05–0.1 mg/kg	10–20	3–5	Histamine release
Hydromorphone	2 mcg/kg/hr	5–10 mcg/kg	5	3–4	Watch units and dosing

D. Adjunctive/Other Therapies

1. Propofol:
 - a. Used as a bridge to extubation
 - b. Usually only used for less than 24–48 hours and at less than 4 mg/kg/hour (67 mcg/kg/minute) because of increased risk of mortality and PRIS (propofol-related infusion syndrome)
 - c. Can cause propofol-related infusion syndrome and hypertriglyceridemia
 - d. Rapid onset (1–2 minutes) and short duration of action (3–15 minutes)
2. Dexmedetomidine:
 - a. α_2 -Agonist more potent than clonidine
 - b. Low respiratory depression (usually none)
 - c. Dose: 0.2–0.7 mcg/kg/hour; however, higher doses are used: 1–2 mcg/kg/hour
 - d. Can cause hypotension and bradycardia by decreasing conduction through the AV node and with bolus dosing
3. Clonidine:
 - a. α_2 -Agonist
 - b. Can use to help wean off medications or as an adjunct to sedation
 - c. Patch can be used.
4. Antihistamines:
 - a. Diphenhydramine can be used for its sedative properties.
 - b. Caution with paradoxical hyper-excitation
5. Ketamine:
 - a. Dissociative amnestic
 - b. Active metabolite
 - c. Causes bronchial smooth muscle relaxation (ideal in patients with asthma)
 - d. Usually few effects on respiratory system
 - e. Can cause emergence phenomena – Use benzodiazepine before
 - f. Intravenous dose: 0.5–2 mg/kg then continuous infusion (0.3–1.2 mg/kg/hour) titrated to effect
6. Barbiturates:
 - a. Usually used as a last-line therapy if other sedative options have failed
 - b. Can lower ICP, so useful in TBI
 - c. Significant hypotension and contains propylene glycol
 - d. Pentobarbital 1-mg/kg bolus followed by a 1-mg/kg/hour infusion
 - e. Long half-life and duration, which can lead to problems when evaluating neurological status or extubating

E. Assessment

1. Can use State Behavioral Scale (SBS) or COMFORT-B scale for sedation
2. Face, Legs, Activity, Cry, Consolability (FLACC) scale or Comfort B scale (alertness, calmness, respiratory response) can be used for pain.

F. Dependence

1. Occurs with the benzodiazepines, opioids, and α_2 -agonists
2. Depends on dose and duration of infusions
3. Various protocols and extremely institution-specific
4. Withdrawal will likely occur if more than 7–9 days on infusions
5. 3–5 days monitor with scale if using high doses
6. Withdrawal is less likely to occur if less than 5 days on infusions
7. Can use the Withdrawal Assessment Tool-1 or Sophia Observation scale for monitoring of withdrawal from benzodiazepines and/or opioids
8. In general, use lorazepam and methadone to wean from sedation.
 - a. Various protocols available and very patient-specific
 - b. Example: Lorazepam 0.1 mg/kg every 6 hours
 - c. Example: Methadone 0.1 mg/kg every 6 hours (every 8, every 12, every 24 hours can also be used, depending on clinical situation)
 - d. Weaning by around 10%–20% every day or every other day
 - e. Can wean over days or weeks, depending on clinical situation

G. Neuromuscular Blockade

1. Uses
 - a. Rapid sequence intubation
 - b. Facilitating mechanical ventilation
 - c. Decreasing oxygen consumption
 - d. To monitor, use train of four.
2. Agents (see Table 4)

Table 4. Agents

Agent	Continuous Infusion Starting Dose (mcg/kg/min)	Bolus Dose (mg/kg)	Onset (min)	Duration (min)	Notes
Succinylcholine	Malignant hyperthermia Not used	2	0.5–1	5–10	Depolarizing, hyperkalemia, not routinely used
Rocuronium	7–12	0.6–1.2	0.7–1	30–60	Used for rapid sequence intubation
Vecuronium	1–2.5	0.1	2–3	30–40	Commonly used
Cisatracurium	1–4	0.15	2	30	Hoffman metabolism: Good in renal and hepatic impairment

3. Adverse effects
 - a. Have adequate sedation first – Neuromuscular blockers provide no sedation or pain control.
 - b. Muscle weakness and atrophy
 - c. Corneal ulcers – Use ocular lubrication.
 - d. Venous thromboembolism (older children)
 - e. Aminoglycosides, β -blockers, corticosteroids potentiate effects of neuromuscular blocking agents

H. ICU Delirium

1. Estimated 25% prevalence
2. Acute cerebral alterations

3. Changes in neurotransmission, cerebral blood flow, and oxidative stress
4. Risk factors
 - a. Infection/inflammatory disorders
 - b. Benzodiazepine exposure (especially midazolam)
 - c. Physical restraints
 - d. Age younger than 2 years
 - e. Need for mechanical ventilation
 - f. Vasopressor medications
5. Assessment:
 - a. Pediatric Confusion Assessment Method for ICU (pCAM-ICU): Older than 5 years
 - b. Preschool Confusion Assessment Method for the ICU (psCAM-ICU): From 6 months to 5 years of age
 - c. Cornell Assessment of Pediatric Delirium (CAP-D(R)): 0–21 years and across developmental levels
6. Treatment:
 - a. Interprofessional PICU bundles including delirium and sedation management can decrease ICU delirium.
 - b. Nonpharmacologic:
 - i. Parents present
 - ii. Look for infection
 - iii. Avoid restraints
 - iv. Music
 - v. Toys
 - vi. Pictures of familiar things (home, school, pets)
 - vii. Normal sleep/wake cycle
 - c. Pharmacologic for refractory delirium – Monitor QTc (corrected QT):
 - i. Haloperidol: 0.15–0.25 mg intravenous load; then 0.05–0.5 mg/kg/day in three or four divided doses (maintenance) – Watch extrapyramidal symptoms, especially dystonic reactions.
 - ii. Risperidone 0.1–0.2 mg oral load; then 0.2–2 mg/day maintenance
 - iii. Olanzapine/quetiapine: Evolving evidence
 - iv. Dexmedetomidine: Emerging evidence
 - v. Limit the use of midazolam

Patient Cases

4. A 6-month-old child undergoes intubation for respiratory syncytial virus pneumonia. She is given fentanyl 1 mcg/kg/hour and midazolam 1 mcg/kg/minute with good sedation. On the second day of sedation, she is recovering from pneumonia and ready for extubation. Which is the most appropriate course for her sedation?
 - A. Discontinue the sedatives.
 - B. Continue mechanical ventilation for another 24 hours while the drips are weaned off.
 - C. Initiate oral methadone and lorazepam.
 - D. Initiate a clonidine patch.
5. A 2-year-old child, on long-term total parenteral nutrition secondary to short gut, presents with an acute viral endocarditis and is subsequently placed on ECMO for cardiac support. He has remained on ECMO for 14 days as his cardiac function recovers. Sedation is achieved with fentanyl 5 mcg/kg/hour and midazolam 6 mcg/kg/minute (0.36 mg/kg/hour). As his heart improves, a decannulation and extubation is planned in 24–36 hours. Which is the most appropriate course for his sedation?
 - A. Discontinue fentanyl and midazolam, and start morphine and lorazepam continuous infusions.
 - B. Wean off fentanyl and midazolam by time of extubation.
 - C. Wean off fentanyl and midazolam by time of extubation, and start a clonidine patch.
 - D. Wean off fentanyl and midazolam by time of extubation, and start lorazepam and methadone.

III. EXTRACORPOREAL MEMBRANE OXYGENATION

A. Introduction

1. Mechanical support after medical support fails
2. Can be used for pulmonary or cardiac failure (may be used after cardiac arrest as a form of CPR [i.e., extracorporeal CPR])
3. Involves venous and arterial cannulation, mechanical ventilation, sedation, and anticoagulation
4. Adverse effects: Thrombotic and hemorrhagic, infections, organ dysfunction, blood transfusions

B. Circuit Design

1. The venous cannula removes blood from the circulation, which then travels through an artificial pump and a membrane oxygenator and returns oxygenated blood to the patient through either venous (VV) or arterial (VA) access.
2. Tubing consists of a polyvinylchloride-based compound contributing to drug binding.
3. Consists of various access points and stopcocks, which are sites of blood stasis potentially resulting in clots; anticoagulation needed
4. Circuit is primed with fluids that are center-specific but usually contain albumin, blood products, heparin, and calcium.
5. The oxygenator allows for the removal of CO₂ and the addition of O₂ into the blood through a hollow fiber polymethylpentene or silicone membrane which can also trap drugs.
6. Can add continuous renal replacement therapy dialysis into the circuit, causing additional removal of drugs
7. Air embolism can occur in the circuit, resulting in air entering the patient. Additions to the circuit such as a bladder (also traps blood clots) can reduce the risk but can also act as a drug reservoir.
8. Newer machines use a centrifugal pump, not a roller as in the past. The patient's SVR can affect blood flow, so management of hypertension is essential.

C. Infection

1. Overall risk of 12% and increases with increasing duration.
2. Universal prophylaxis not established; usually gram-positive coverage to cover skin flora

D. Anticoagulation

1. Needed because of the formation of clots secondary to activation of the clotting cascade from the artificial circuit
2. Clot formation in the circuit is the leading cause of mechanical issues with the machine.
3. Bleeding can occur, and generalized bleeding (into organs) should be treated with platelets, reduced anticoagulation dose, and recombinant factor VII (use with caution because of clotting)
4. Heparin:
 - a. Most widely used anticoagulant in ECMO
 - b. Binds to antithrombin and inhibits factors Xa, IXa, XIa, XIIa, and IIa (thrombin)
 - c. 50- to 100-unit/kg bolus dose at the time of cannulation; when activated clotting time decreases to less than 300 seconds, then continuous infusion is started at 20 units/kg/hour
 - d. Monitor for heparin-induced thrombopenia, and if it occurs, can use argatroban or bivalirudin (some centers use these agents more frequently)
5. Monitoring:
 - a. Activated clotting time:
 - i. Has point-of-care testing useful in ECMO
 - ii. Measures clotting of whole blood
 - iii. In general, titrate to range of 180–220 seconds, but mainly focus on patient bleeding and clot formation in the circuit; this is highly variable by center

- b. Antifactor Xa (anti-Xa) assay: Increasing use in centers
 - i. 0.3–0.7 international unit/mL goal, with some centers using goals of 0.7–1.1 international units/mL
 - ii. Measures heparin, antithrombin, and conversion of factor X
 - c. Activated partial thromboplastin time: Measures hemostasis without cellular components. Not as consistent because of poor correlation with anti-Xa in children
- E. Overall Drug Changes (see Table 5)
- 1. Volume of distribution:
 - a. Increased because of increased circulating blood volume
 - b. Can be increased 5%–400%
 - 2. Loss of drug in circuit:
 - a. Caused by adsorption to the tubing or oxygenator membrane
 - b. Most significant for lipophilic drugs
 - c. Studies have reported up to 99% drug loss for some drugs.
 - 3. Clearance: Usually decreased by 0%–50% of cleared drugs because of decreased renal function and potentially decreased liver function

Table 5. Drugs in ECMO

Drug	Vd	Clearance	Adsorption to Circuit	Notes
Aminophylline	↑	↓		
Bumetanide	↑	↓		
Cefotaxime	↑	↓		
Fentanyl	↑	↓	70%–80% loss	
Fluconazole	↑ 50%	↓	2%	
Furosemide	↑		70% loss	
Gentamicin	1.5–2 x ↑	2 x ↓	10% loss	Similar with tobramycin
Midazolam	3–4 x ↑	↓	70% loss	
Morphine	2 x ↑	↓	30% loss	
Phenobarbital	↑ slightly		20% loss	
Propofol	↑		98% loss	
Sildenafil	↑			Still within dosing range
Vancomycin	↑ slightly	↓	30% loss	
Voriconazole			70% loss	Caution with renal insufficiency

This is based on limited studies, case reports, or animal data. This chart is also incomplete because of lack of data, insufficient data, or no pharmacokinetic changes noted in ECMO.

Vd = volume of distribution.

- F. Medication Safety
- 1. Drugs administered directly into the circuit can have delayed mixing and a greater chance of being sequestered by individual components.
 - 2. Using high-alert medications such as heparin
 - 3. Loss in the circuit is usually greater during the first two or three doses and decreases with subsequent doses.

4. Circuit changes are associated with a loss of blood and potentially drug bound to old tubing, affecting dosing post-circuit change.
5. Intravenous lipid emulsion infused into the circuit can cause cracking and clots in the circuit. Recommendations are to infuse intravenous lipid emulsions to the patient and not the circuit.

Patient Case

6. A 13-year-old female patient with a long history of viral cardiomyopathy is in the PICU and on mechanical ventilation secondary to community-acquired pneumonia. All laboratory values are normal (SCr 0.7 mg/dL). The patient's medications include fentanyl continuous infusion 1 mcg/kg/hour, midazolam 0.1 mg/kg/hour, and vancomycin 15 mg/kg/dose every 8 hours. The vancomycin trough this morning was 10 mcg/mL (obtained at the appropriate time and before the fourth dose). The next day, the patient's ejection fraction decreased to 3% and was unable to perfuse her organs. The decision was made to initiate ECMO. Which is the most appropriate management strategy for this patient's medications now that she is on ECMO? (Assume monitoring of vancomycin concentrations.)
 - A. Increase vancomycin only.
 - B. Increase fentanyl only.
 - C. Increase both vancomycin and fentanyl.
 - D. No changes needed to medication.

IV. CARDIAC ARREST

- A. Introduction
 1. Cardiac arrest in children usually starts with respiratory arrest.
 2. Systemic hypoxemia, hypercapnia, and acidosis lead to bradycardia, hypotension, and cardiac arrest. Ventricular tachycardia (VT)/VF: 5%–15% of arrests
- B. Intraosseous Administration
 1. All pediatric advanced life support (PALS) medications can be given by this route.
 2. Give saline flush afterward to counteract delayed drug distribution because of depot effect.
- C. ET Administration
 1. Lipid-soluble drugs can be administered; LEAN: lidocaine, epinephrine, atropine, naloxone
 2. Usually double the dose, except for epinephrine, which is 10 times the intravenous dose
 3. Follow dose with 5 mL of saline flush and five ventilations.
- D. Medications
 1. Adenosine:
 - a. Causes atrioventricular (AV) block
 - b. Used in supraventricular tachycardia (SVT)
 - c. Double-barrel administration: RAPID intravenous push; then rapid saline push
 - d. Administer close to the heart; use peripheral line closest to the heart (central line, if available – some data).
 - e. Not with Wolff-Parkinson-White and wide complex tachycardia
 - f. Dose: 0.1 mg/kg (max 6 mg); then 0.2 mg/kg (max 12 mg)

2. Amiodarone:
 - a. Slows AV conduction, widens QRS (α - and β -blocking)
 - b. Can cause QT prolongation
 - c. Administer over 20–60 minutes if patient has a pulse; should dilute 2.5 mg/mL, if peripheral, or up to 6 mg/mL, if central
 - d. Administer rapid intravenous push if VF or VT; can give undiluted
 - e. Hypotension related to infusion rate
 - f. Contains iodine
 - g. Dose: 5 mg/kg (maximum dose 300 mg)
3. Atropine:
 - a. Parasympatholytic: Increases AV conduction by blocking acetylcholine
 - b. Less than 0.1 mg causes paradoxical bradycardia (but may not when premedicated for intubation)
 - c. Used in bradycardia caused by increased vagal tone or primary AV block
 - d. Given undiluted rapid intravenous push
 - e. Dose: 0.02 mg/kg (minimum dose 0.1 mg)
 - f. Can be used as a pre-med for intubation when high risk of bradycardia, 0.02 mg/kg with no minimum dose
4. Calcium:
 - a. Used only if hypocalcemia, hypermagnesemia, hyperkalemia, or calcium channel blocker overdose
 - b. Calcium chloride is preferred to calcium gluconate because larger rise in ionized calcium
 - c. Calcium gluconate if peripheral line
 - d. Can give over 10–20 seconds
 - e. Dose: Calcium chloride 20 mg/kg; Calcium Gluconate 50–100 mg/kg
5. Epinephrine:
 - a. α -Agonist that causes vasoconstriction, increasing coronary perfusion pressure
 - b. Pulseless VT, VF, asystole, pulseless electrical activity (PEA), or bradycardia
 - c. Do not administer with bicarbonate because of inactivation of epinephrine
 - d. Dose: Rapid infusion of 0.1 mg/mL solution intravenously/intraosseously 0.01 mg/kg (0.1 mL/kg)
 - e. ET tube: Use 1 mg/mL solution 0.1 mg/kg (0.1 mL/kg)
6. Glucose:
 - a. Low glycogen stores, especially in infants
 - b. Give intravenous bolus if hypoglycemic
 - c. Dose: 0.5–1 g/kg
7. Lidocaine:
 - a. Pulseless VT/VF
 - b. Suppresses automaticity and conduction
 - c. Dose: 1 mg/kg; then 20–50 mcg/kg/minute
8. Magnesium sulfate:
 - a. Used in hypomagnesemia and torsades de pointes
 - b. Causes coronary vasodilation, improving myocardial perfusion
 - c. Causes hypotension during rapid administration: Infuse over 5–20 minutes (bolus if no pulse)
 - d. Dose: 25–50 mg/kg
9. Procainamide:
 - a. Decreases conduction
 - b. Used in SVT
 - c. Infuse over 30–60 minutes.
 - d. Causes hypotension, heart block, and QT prolongation
 - e. Dose: 15 mg/kg

10. Sodium bicarbonate:
 - a. Not recommended for routine use (can decrease cardiac function)
 - b. Can decrease the effectiveness of epinephrine
 - c. Use in toxicology or hyperkalemia.
 - d. Can cause an intracellular acidosis
 - e. 1-mEq/mL intravenous push in children; 0.5 mEq/mL in infants
 - f. Dose: 1 mEq/kg
11. Vasopressin:
 - a. Refractory cardiac arrest
 - b. Can increase cardiac and cerebral blood flow
 - c. Dose: 0.4 units/kg

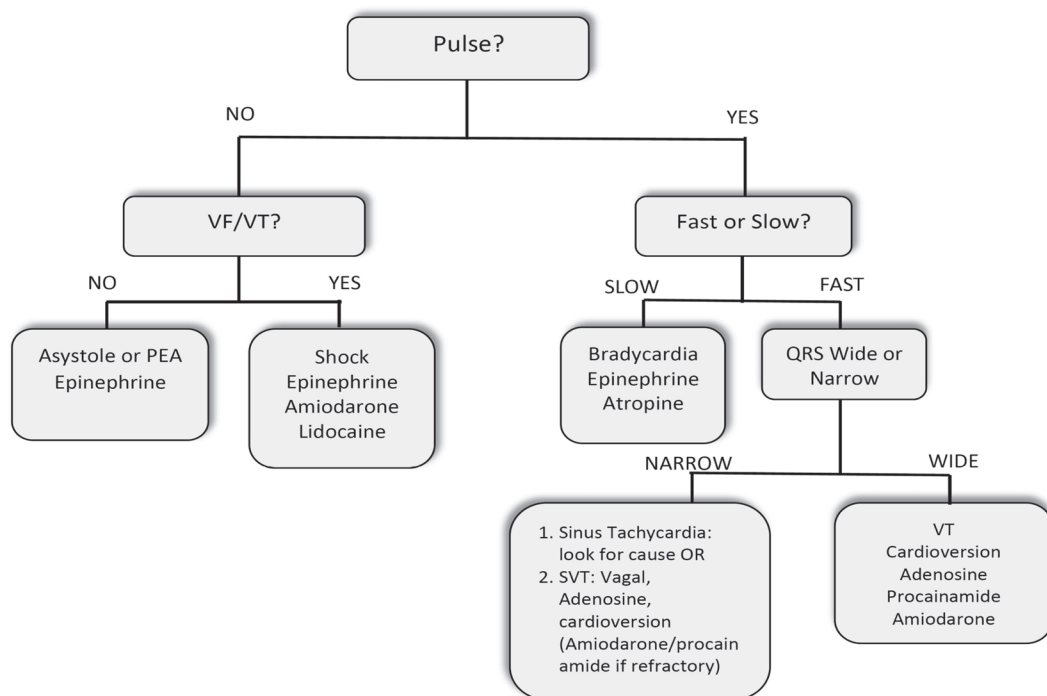


Figure 2. Overall flowchart.

PEA = pulseless electrical activity; SVT = supraventricular tachycardia; VF = ventricular fibrillation; VT = ventricular tachycardia.

- E. Rhythms: See overall flowchart.
 1. Pulseless arrest: VT, VF, asystole, PEA
 - a. H's and T's
 - i. Hypovolemia
 - ii. Hypoxia
 - iii. Hydrogen ions (acidosis)
 - iv. Hypoglycemia
 - v. Hypo/hyperkalemia
 - vi. Hypothermia
 - vii. Tension pneumothorax
 - viii. Tamponade (cardiac)
 - ix. Toxins
 - x. Thrombosis (pulmonary or cardiac)

- b. Treatment:
- Cycles of CPR and epinephrine every 3–5 minutes
 - If VF or VT, then shockable rhythm: 2 J/kg and then 4 J/kg for other shocks if unsuccessful – Can also start with 4 J/kg and increase subsequent shocks up to a maximum of 10 J/kg
 - Use amiodarone or lidocaine after third shock.
 - If torsades de pointes: Use magnesium.

Pediatric Cardiac Arrest Algorithm

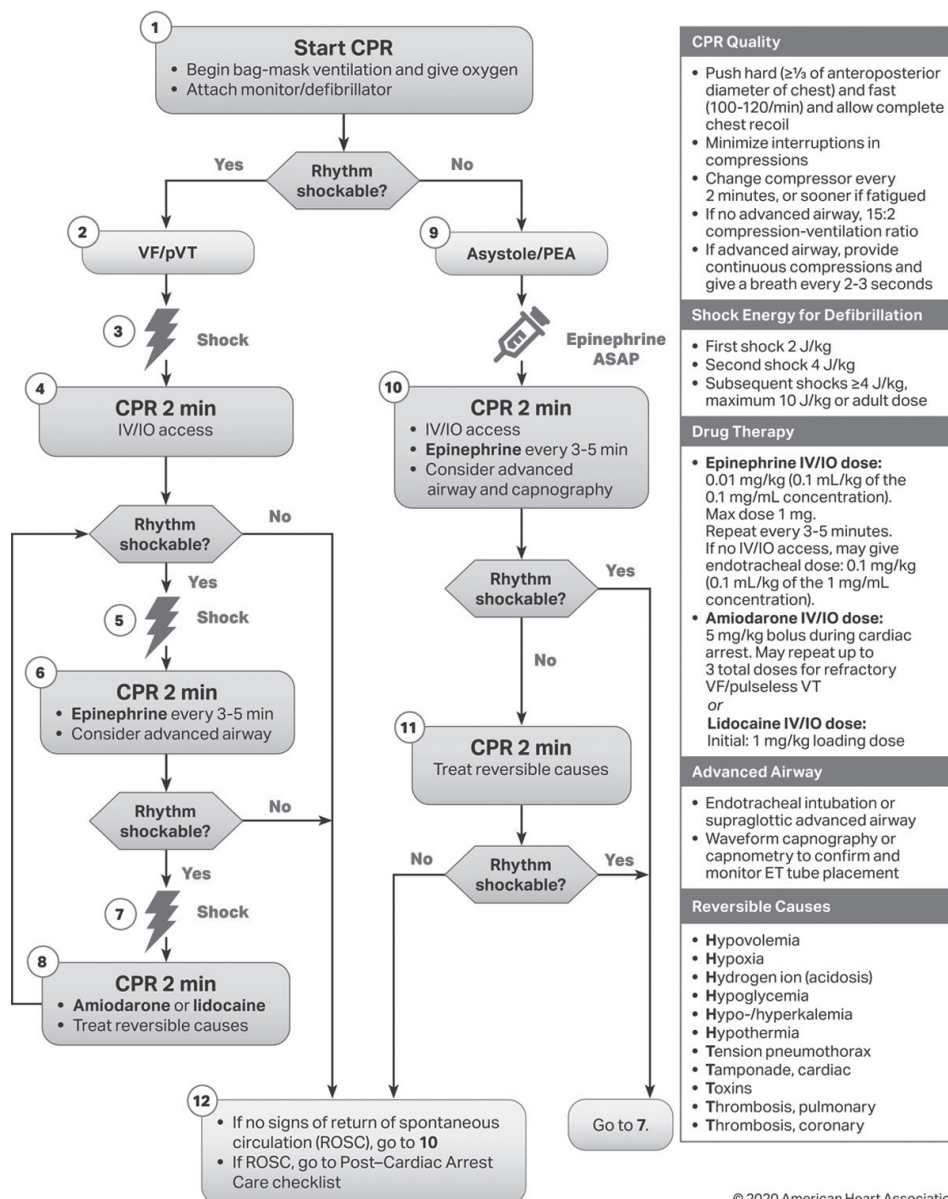


Figure 3. Pediatric cardiac arrest algorithm.

CPR = cardiopulmonary resuscitation; ET = endotracheal; IO = intraosseous; IV = intravenous; pVT = pulseless ventricular tachycardia; ROSC = return of spontaneous circulation.

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2. Bradycardia:
 - a. Has a pulse but low perfusion (mental status changes, hypotension, shock)
 - b. Heart rate less than 60 beats/minute: Initiate CPR.
 - c. If no response, give epinephrine; fix underlying cause (hypoxia, hypoglycemia, acidosis, etc)
 - d. If caused by vagal stimulation, intoxication, or primary AV block, then atropine

Pediatric Bradycardia With a Pulse Algorithm

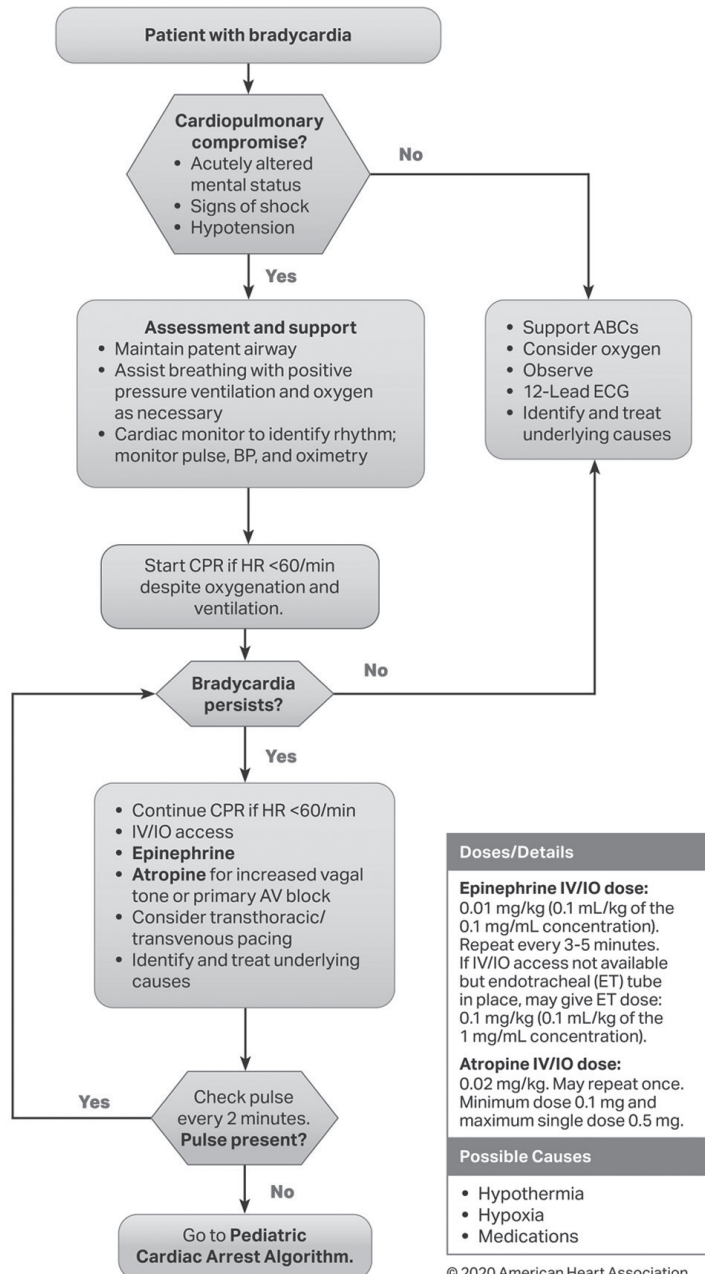


Figure 4. Pediatric bradycardia with a pulse algorithm.

ABC = airway, breathing, and circulation; AV = atrioventricular; BP = blood pressure; ECG = electrocardiogram.

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3. Tachycardia:
 - a. Narrow QRS: 0.09 second or less
 - i. Sinus tachycardia: Treat cause.
 - ii. SVT:
 - (a) Vagal stimulation (ice, Valsalva maneuver)
 - (b) Adenosine; can use verapamil in older children
 - (c) Synchronized cardioversion 0.5–1 J/kg; consider sedation prior
 - (d) Can use amiodarone or procainamide after second shock
 - b. Wide QRS (0.09 seconds or more):
 - i. Cardiopulmonary compromise: If yes, then cardioversion
 - ii. If no, then can use adenosine if QRS monomorphic
 - iii. Amiodarone or procainamide

Pediatric Tachycardia With a Pulse Algorithm

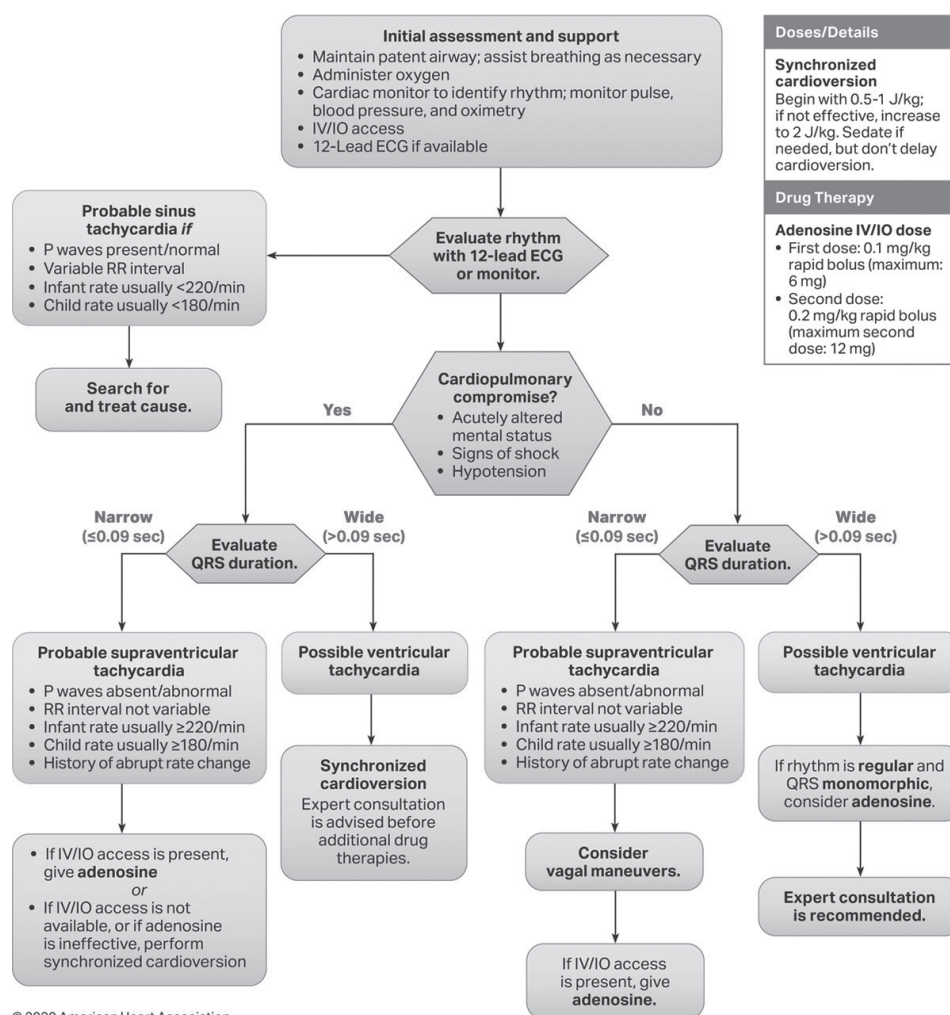


Figure 5. Pediatric tachycardia with a pulse algorithm.

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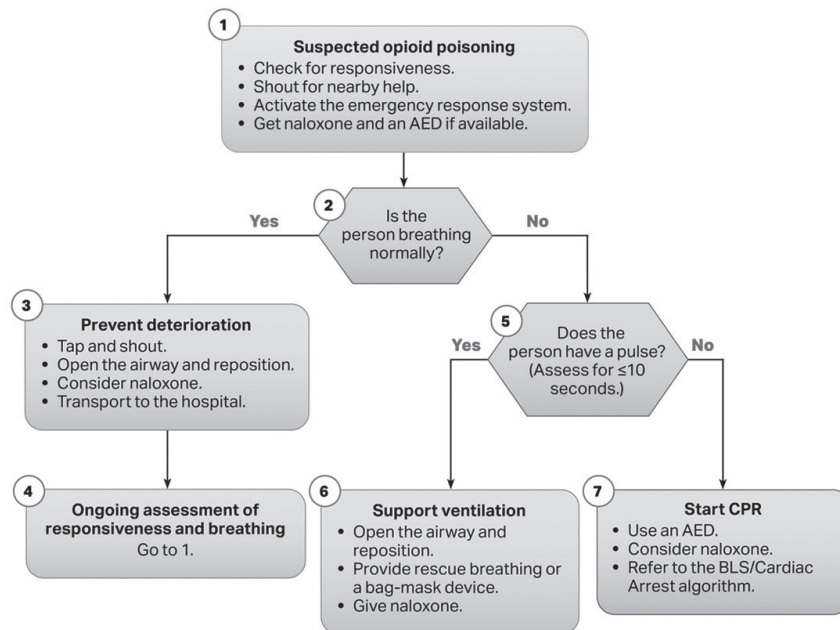
F. Special Considerations

1. Single ventricle physiology
 - a. Goal is to increase systemic oxygen delivery through the use of oxygen and systemic vasodilators.
 - b. Can use adrenergic antagonists/vasodilators (e.g., sodium nitroprusside or phentolamine) and/or phosphodiesterase type III inhibitors (i.e., milrinone).
 - c. If shunt obstruction, give 50–100 unit/kg heparin bolus while awaiting surgical intervention and vasoactive agents (e.g., phenylephrine, norepinephrine, epinephrine) to maximize shunt perfusion.
2. Pulmonary hypertension crisis (see Cardiology chapter)
 - a. Inhaled nitric oxide or prostacyclin
 - b. Analgesics, sedatives, and neuromuscular blocking agents

G. Opioid-Related Respiratory and Cardiac Arrest

1. Perform basic or advanced life support as indicated, including compressions plus ventilation.
2. Patients with a pulse and nonnormal breathing or just gasping, administer naloxone. Do not delay CPR for arrival of naloxone.
 - a. Pure opioid antagonist; half-life 30–120 min
 - b. Preferred routes intramuscularly, intranasally, or intravenously
 - c. Can be given subcutaneously, intraosseously, and endotracheally
 - d. Dosing:
 - i. Intravenously <20 kg: dose 0.1 mg/kg/dose; >20 kg: dose 2 mg/dose repeated every 2–3 minutes; reversal of respiratory depression from therapeutic opioid dosing 0.001–0.015 mg/kg/dose
 - ii. Endotracheally 2–3 times intravenous dose
 - iii. Intramuscularly 0.4 or 2 mg auto injector
 - iv. Intranasally 4 mg spray as single dose

Opioid-Associated Emergency for Healthcare Providers Algorithm



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Figure 6. Opioid-associated emergency for healthcare providers algorithm.

AED = automated external defibrillator; BLS = basic life support.

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H. Post–Cardiac Arrest Care

1. Patient may need pain control and sedation; neuromuscular blocking agents, if needed
2. Patient will likely have cardiovascular compromise; agent for support depends on patient
3. Epinephrine, dopamine, norepinephrine, dobutamine, milrinone, sodium nitroprusside as needed
4. Targeted temperature management: Avoid hyperthermia. Some use hypothermia which can affect the pharmacokinetics of some drugs.
5. Patient may have had renal or hepatic injury, so caution with drugs

I. Medication Safety

1. High-intensity situation: Potential for errors
2. Lots of potential for confusion and multiple simultaneous drug orders: Look to team leader for therapy (usually PICU attending).
3. Weight of child sometimes unknown; use of tapes (Broselow) useful in estimating equipment size and medication doses
4. Knowledge of algorithms: Understanding of clinical situations and drugs normally used to reduce errors
5. Communication: Verbal order – Read back with team.
6. Double-check: Many high-alert medications used; double-check dosing, if possible
7. Labeling: Usually small space to work in; label syringes accurately to prevent errors
8. Many forms of drugs: Epinephrine 1 mg/mL versus 0.1 mg/mL

Patient Case

Questions 7–9 pertain to the following case.

A code is called on a 7-year-old child who was extubated yesterday after a 6-day stint of respiratory syncytial virus pneumonia. The team arrives at the scene and finds no pulse. Chest compressions are begun, and the patient is placed on a monitor. The monitor reveals PEA. The nurses cannot establish peripheral intravenous access after three attempts (10 minutes), and the patient does not have a central line. They are setting up for an emergency intubation, but they have not yet begun.

7. Which is the most appropriate next course of action for this patient?
 - A. Continue chest compressions until intravenous access is obtained.
 - B. Interrupt the first round of compressions to establish ET access for drugs.
 - C. Administer 2–10 times the intravenous dose of a vasoactive medication sublingually.
 - D. Establish intraosseous access and administer the same intravenous dose of the vasoactive medication.
8. Access is obtained, and the monitor now reveals VF. Which is the most appropriate initial drug therapy?
 - A. Adenosine.
 - B. Epinephrine.
 - C. Atropine.
 - D. Amiodarone.

Patient Case (*continued*)

9. The team is able to resuscitate the patient and has increased perfusion and pulses. The next day, the child begins to have some mental status changes, and the monitor reveals a wide QRS complex tachycardia. Which is the most appropriate therapy for this child?
- A. Adenosine.
 - B. Amiodarone.
 - C. Procainamide.
 - D. Cardioversion.

V. TRAUMATIC BRAIN INJURY**A. Background**

- 1. 35,000 hospitalizations and 2000 deaths annually from TBI
- 2. 20% of patients need ICP monitoring; 20% mortality
- 3. Risk factors: Adolescents, male sex, white race, urban areas

B. Pathophysiology

- 1. Primary injury: Wear your helmet and seatbelt.
 - a. Rapid deceleration and rotation forces
 - b. Hematoma
 - c. Hemorrhage
 - d. Diffuse axonal injury: Poor survival and vegetative state
- 2. Secondary injury (all therapy geared at preventing this)
 - a. All about the cerebral perfusion pressure (CPP) = mean arterial pressure (MAP) – intracranial pressure (ICP); $CPP = MAP - ICP$
 - b. Inflammation and excitatory mediators (TNF α and IL-1 β) increase edema.
 - c. Edema severe and widespread, increasing ICP
 - d. Glutamate (excitatory amino acid) released, activating *N*-methyl-D-aspartate (NMDA) receptors, and calcium moves into cells
 - e. Calcium causes release of nitric oxide and oxygen-free radicals: Together, cause lipid peroxidation
 - f. Leads to cell death

C. Treatment

- 1. $CPP = MAP - ICP$
- 2. CPP target 40–50 mm Hg (children lower end, adolescents higher end)
- 3. Maintain CPP by keeping MAP normal for age and ICP low; hypotension = poor outcome
- 4. MAP:
 - a. Aggressive fluid management: Want euvolemia and replacement of blood and fluids after injury
 - b. Use saline – Osmolarity needed in TBI; albumin increases mortality in adults
 - c. Vasopressors if MAP still low after fluids
 - i. Dopamine, norepinephrine, and phenylephrine all useful
 - ii. Norepinephrine and phenylephrine: Larger increase in blood pressure
- 5. ICP:
 - a. Decreased perfusion to tissue, decreased oxygen delivery
 - b. ICP greater than 20 mm Hg (greater than 15 mm Hg in infants) for more than 5 minutes: Treat.

-
- c. Hyperosmolar therapy: Titrated to a goal of less than 360 mOsm/L
 - i. Hypertonic saline: Goal sustained sodium less than 160 mEq/L. Some have used short-term (less than 72 hours) goal up to 170–180 mEq/L.
 - (a) Changes osmolar gradient, cell membrane resting potential, cell volume
 - (b) Decreases inflammation and release of atrial natriuretic peptide
 - (c) Usually 3% saline: Central line preferred but can use peripheral if needed
 - (d) 2- to 5-mL/kg (6–10 mL/kg has been used) bolus; then 0.1- to 1-mL/kg/hour infusion
 - (e) Adverse effects: Rebound ICP spikes, central pontine myelinolysis, renal dysfunction, hyperchloremic metabolic acidosis
 - (f) Evidence for 23.4% saline
 - ii. Mannitol:
 - (a) Reduces blood viscosity through reflex vasoconstriction: Works quickly and lasts 1 hour
 - (b) Osmolar agent: Works in 15 minutes and lasts 6 hours
 - (c) ICP spikes: 0.25–0.5 g/kg every 6 hours (higher doses used clinically)
 - (d) Adverse effects: Accumulation in injured section, causing reverse osmotic gradient and increasing ICP
 - (e) Not as effective as saline
 - (f) Can precipitate in vial; monitor; filter needed for administration
 - iii. Barbiturates:
 - (a) Cause decreased cardiac output and hypotension: Use in hemodynamically stable
 - (b) Cause metabolic suppression, decreasing ICP
 - (c) Lower oxygen-free radicals and decrease lipid peroxidation
 - (d) Pentobarbital usually used (thiopental studied) 5- to 10-mg/kg bolus; then 1- to 2-mg/kg/hour infusion
 - (e) Target burst suppression, not a particular drug concentration
 - iv. Sedation/pain:
 - (a) Intubated patients will need sedation.
 - (b) Anticonvulsant and antiemetic properties (seizures and vomiting increase ICP)
 - (c) Decrease cerebral oxygen demands through decreased pain and agitation
 - (d) All sedative agents cause hypotension: CPP = MAP – ICP (keep MAP normal).
 - (e) Use standard sedatives of benzodiazepines and opioids.
 - (f) Propofol: Good agent for TBI because of short half-life; not for more than 24–48 hours and caution with propofol-related infusion syndrome
 - (g) Ketamine: NMDA receptor antagonist blocking glutamate and may be neuroprotective; can increase MAP through catecholamine release; main use is in patients already on sedatives and undergoing a procedure
 - (h) Dexmedetomidine: α_2 -Agonist; can cause hypotension; has neural cell protection by activating protein kinases 1 and 2; can be used as adjunct in TBI
 - (i) Neuromuscular blockers: Reduce intrathoracic pressure, increasing brain venous return, and decrease metabolic oxygen demands; succinylcholine can increase ICP
 - 6. Other management strategies/concerns:
 - a. Hyperventilation: Can decrease ICP
 - b. Hypothermia: Controversial, but avoid hyperthermia
 - c. Initiate early nutrition support within 72 hours and full nutrition by 1 week.
 - d. Avoid hypoglycemia and hyperglycemia.
 - e. Phenytoin prophylaxis for seizures can be considered at a free-level target of 1–2 mcg/mL (emerging data and increased use of levetiracetam).
-

Patient Case

Questions 10 and 11 pertain to the following case.

A 5-year-old girl was an unrestrained passenger in a motor vehicle collision. Having sustained a significant TBI with a Glasgow Coma Scale score of 3, she is brought to the emergency department after undergoing intubation at the scene. An intracranial monitor is placed, which reveals an ICP of 30 mm Hg. She is hypotensive and tachycardic. After initial fluid resuscitation, her blood pressure normalizes, but she remains tachycardic. She will likely require intubation for more than 7 days.

10. Which would be the most appropriate therapy for managing her tachycardia?
 - A. Propofol infusion for length of intubation.
 - B. Midazolam and fentanyl infusions for length of intubation.
 - C. Ketamine infusion for length of intubation.
 - D. Vecuronium infusion for length of intubation.
11. Laboratory values are as follows: sodium 137 mEq/L, potassium 4.1 mEq/L, chloride 100 mEq/L, bicarbonate 25 mEq/L, blood urea nitrogen 20 mg/dL, and SCr 0.6 mg/dL. Her ICP is still 30 mm Hg. Which is the most appropriate initial therapy for managing her ICP?
 - A. Mannitol 0.5 g/kg every 6 hours.
 - B. 10-mL/kg bolus of 3% saline.
 - C. 0.2-mL/kg/hour infusion of 3% saline.
 - D. 5-mg/kg pentobarbital bolus.

VI. BURNS

- A. Background
 1. 11 million people each year in the world; 35% are children
 2. 6% of all pediatric injuries; 3.9/100,000, mortality worse in low-income countries
- B. Pathophysiology
 1. Burned cells have changes in transmembrane potential.
 2. Sodium ATPase function changes, leading to increased intracellular sodium: Cellular edema and hypervolemia
 3. Inflammatory mediator release: Cytokines, histamine, prostaglandins, substance P, and oxygen-free radicals: Local vasoconstriction, systemic vasodilation, and decreased myocardial contractility
 4. Capillary permeability: Fluids and proteins move to interstitial space.
 5. Hypermetabolic state: Released catecholamines, hyperglycemia, insulin resistance, lipolysis
 6. Greater than 20% total body surface area (TBSA) increased metabolic state, fluid requirements, and nutritional needs

C. Pharmacokinetic Changes in Burns

1. Absorption: Oral absorption decreased immediately postburn due to peripheral and splanchnic vasoconstriction. During hypermetabolic state, increased oral absorption due to increased perfusion.
2. Distribution
 - a. Larger volume of distribution due to capillary leak, edema, and large fluid resuscitation
 - b. Decreased protein binding from lower levels of albumin in burn patients due to fluid loss from burn wounds, decreased hepatic synthesis, and increased catabolism
3. Metabolism: Increased through metabolic state. However, early liver dysfunction can occur in burn patients
4. Renal clearance can be variable; hyperdynamic state can increase renal blood flow and increase renal clearance.

D. Treatment

1. Fluids:
 - a. Up to 6 mL/kg per percent TBSA replacement warmed crystalloid in first 24 hours after injury in children
 - b. 3–4 mL/kg per percent TBSA replacement in adults
 - c. Replacement same as dehydration protocol: One-half in first 8 hours, one-half over next 16 hours
 - d. Deep burns, late resuscitation, and inhalation burns require more
 - e. No set fluid, but lactated Ringer solution is standard for children and adults
 - f. Can use albumin-assisted resuscitation to reduce incidence of fluid creep and increase oncotic pressure
2. Hormone therapy:
 - a. Hypermetabolic response results in overall muscle wasting.
 - b. Oxandrolone: Synthetic hormone similar to testosterone-enhancing protein synthesis. 0.1 mg/kg twice daily can increase muscle mass and decrease resting energy expenditure in children.
 - c. Growth hormone: Anabolic agent decreases catabolism in damaged tissue. Potential increase in healing time of skin graft but not major outcomes
3. β -Blockers:
 - a. Catecholamine release causes tachycardia and increased cardiac demands.
 - b. Propranolol decreases response, decreases resting energy expenditure, and increases lean body mass: 1 mg/kg/day titrated to 4–6 mg/kg/day to a goal of a 15% decrease in heart rate
4. Nutrition and glucose:
 - a. Early nutrition (first day of injury) may be beneficial.
 - b. May need additional selenium
 - c. Data suggest less than 150 mg/dL for glucose goal concentration (probably 100–130 mg/dL).

Patient Case

12. A 3-year-old girl (weight 15 kg) had a severe scald injury to 60% of her TBSA. Which is the most appropriate replacement rate for fluids during the next 24 hours?
- A. 113 mL/hour for 24 hours.
 - B. 169 mL/hour for 8 hours; then 84 mL/hour for 16 hours.
 - C. 225 mL/hour for 24 hours.
 - D. 338 mL/hour for 8 hours; then 169 mL/hour for 16 hours.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES**1. Answer: A**

This patient has a fever with a leukocytosis, classifying him as having SIRS (Answer A is correct). If there were laboratory abnormalities or the presence of an infection, he would be classified as having sepsis (Answer B is incorrect). Hypotension would indicate septic shock (Answer D is incorrect). Sepsis-associated organ dysfunction (Answer C) would be correct if there were other organ system dysfunction.

2. Answer: D

The child's ankle has a warm area around it now, which appears to be an infection, placing him in sepsis. He is also hypotensive now, which signifies decompensated septic shock (Answer D is correct). Because the patient is thought to have an infection, Answer A is incorrect. Answer B is incorrect because he has cardiovascular dysfunction. Answer C would be correct if there were other organ system dysfunction.

3. Answer: C

Proper treatment is 10–20 mL/kg of lactated Ringer solution up to three times. The team was able to do only two boluses when water began filling the patient's lungs. Crackles suggest that further fluid boluses will negatively affect respiratory status. Because further fluids would only worsen the pulmonary edema, this therapy is now contraindicated (Answer D is incorrect). A vasopressor is the next treatment modality for him. Milrinone is used in increased SVR and decreased cardiac output states. However, this patient has decreased SVR, making milrinone incorrect (Answer B is incorrect). Dobutamine is usually reserved for cardiac dysfunction because other agents have more impact on SVR (Answer A is incorrect). Norepinephrine is a first-line agent for septic shock (Answer C is correct).

4. Answer: A

This patient has been on a low level of sedation and has been on continuous infusions for only 2 days. Withdrawal is unlikely, so discontinuing the sedatives would be appropriate (Answer A is correct). Continuing an intubation while drips are weaned is inappropriate because there are many ways to prevent withdrawal, if needed, other than prolonging mechanical ventilation (Answer B is incorrect). Methadone and lorazepam are

not needed because withdrawal is unlikely (Answer C is incorrect). A clonidine patch could help if there were issues with weaning, but they are not needed in this case (Answer D is incorrect).

5. Answer: D

This patient has been on ECMO support for more than 2 weeks with a great deal of sedation (because of the circuit not all going to the patient), and ECMO and mechanical ventilation will be withdrawn. Answer A would not greatly help but could be used if the patient were difficult to sedate and switching agents might be beneficial. Slowly weaning off the drips over 2–3 days or so will likely be insufficient to prevent withdrawal. Answer B is incorrect because, before extubation, a good level of sedation should be achieved to prevent the child from self-extubation or, worse, self-decannulation. The clonidine patch would be an adjunct to use; however, it will take 72 hours to take full effect and is not appropriate while trying to decannulate (Answer C is incorrect). Because the patient will need some sort of agents to prevent withdrawal and needs to come off of the drips, Answer D is correct.

6. Answer: C

In general, there is an increased volume of distribution in ECMO and a decreased clearance of drugs. Fentanyl is lost extensively in the circuit. During the initial cannulation, major increases in dosing may be required to sedate the patient adequately (Answer D is incorrect). Using vancomycin can be difficult. There will be an increased volume of distribution, requiring more drug. After initial deployment on ECMO, the patient would need increased fentanyl and vancomycin (Answer C is correct). Answers A and B are incorrect as they only address one medication.

7. Answer: D

This is an emergency, and the only treatment for it is intravenous drugs. Nondrug therapies such as defibrillation do not work in PEA. Answer A is incorrect because the nurses have already tried three times (for 10 minutes) to establish access. Answer B is incorrect because one of the basics of advanced life support is good basic support, including chest compressions, and interrupting compressions to obtain ET access is not

appropriate. The team is setting up for intubation but has not begun the process. Chest compressions should be interrupted for the least amount of time needed. Answer C is incorrect because sublingual administration has no real role in cardiac arrest. Answer D is correct because intraosseous administration is a quick way to establish access, and the code medications have been studied and used this way.

8. Answer: B

In VF, epinephrine is the drug of choice (Answer B is correct), together with defibrillation (although the question specifically asked for drug therapy, defibrillation is optimal in this setting). The other options (adenosine and atropine) are not used in VF (Answers A and C are incorrect). Amiodarone (Answer D) would be an option after the first round of epinephrine has failed.

9. Answer: D

This patient is having some type of VT. Because the patient is also having mental status changes, the condition is considered cardiopulmonary compromise. The immediate option is synchronized cardioversion (Answer D is correct). If the patient were not having signs of compromise, adenosine (if regular rhythm and QRS monomorphic) (Answer A), amiodarone (Answer B), or procainamide (Answer C) would be options, depending on the situation and rhythm.

10. Answer: B

This patient has been adequately resuscitated with fluids but remains tachycardic likely because of her pain and sedation needs. Answer B is correct; standard sedation with midazolam and fentanyl would be appropriate to initiate. Answer A is incorrect because propofol should not be used for more than 24–48 hours in children. Answer C could be an option, but in TBI, it has been studied only in procedural sedation as an adjunct. Answer D is incorrect because paralyzing a patient without adequate sedation is inappropriate.

11. Answer: B

According to these laboratory values, all of the patient's tests are within normal range. However, her sodium concentration, though normal, is too low for a patient with TBI. Strategies to increase the sodium to 160 mEq/L or higher should be used. A bolus is a quick way to increase the patient's sodium and lower the

increase in ICP initially (Answer B is correct). Answer C is incorrect; she could be placed on a 0.2-mL/kg/hour infusion of 3% saline after the saline bolus because it would not rapidly lower her ICP. Mannitol is an appropriate choice; however, evidence points toward using saline over mannitol (Answer A is incorrect). Using a pentobarbital bolus would be appropriate when the other options have failed (Answer D is incorrect).

12. Answer: D

The patient's replacement rate for fluids is up to 6 mL/kg. See self-assessment question 2: $6 \text{ mL} \times 15 \text{ kg} \times 60 \text{ TBSA} = 5400$. Divided in half, this would equate to 2700 mL in the first 8 hours = 338 mL/hour for 8 hours. For the second half, 2700 mL in the next 16 hours = 169 mL/hour for 16 hours (Answer D is correct). Answer A gives only about one-half of what the child needs. Answer B is incorrect for the same reason as Answer A and gives about 3 mL/kg instead of 6 mL/kg. Answer C gives the total daily requirement but does not account for the profound immediate dehydration.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: D**

The patient is in septic shock, as evidenced by the hypotension. After appropriate fluid administration and with continued hypotension, vasopressor therapy is indicated. In the previous guidelines, the answer would have been dopamine because the patient is in “cold” shock. However, dopamine has been replaced with epinephrine or norepinephrine as first-line therapy (Answer A is incorrect; Answer D is correct). Milrinone is reserved for patients with decreased cardiac function and/or pulmonary hypertension. Because this patient already has hypotension, milrinone would further decrease SVR (Answer C is incorrect). Vasopressin is reserved for when other alternatives have failed (Answer B is incorrect).

2. Answer: B

The equation is 6 mL/kg per percent TBSA: $6 \text{ mL/kg} \times 30 \text{ kg} \times 40(\text{TBSA}) = 7200$. Then, treatment is similar to dehydration replacement. Take the total and divide it by half. The first half is replaced in the first 8 hours, and the second half is replaced over the next 16 hours: $7200/2 = 3600 \text{ mL}$; 3600 mL over first 8 hours = 450 mL/hour for 8 hours; 3600 mL over the next 16 hours = 225 mL/hour for 16 hours (Answer B is correct). Answer A gives the same amount during the 24-hour period but does not solve the immediate problem of profound dehydration. Answer C is just switched around. Answer D would be for a total of 3 mL/kg per percent TBSA, which would provide inadequate resuscitation for the patient.

3. Answer: B

Fentanyl has an increased volume of distribution (Answer A is incorrect), can be adsorbed into the circuit by almost 80% (Answer B is correct), and has decreased clearance (Answer C is incorrect). Fortunately, because this is a continuous infusion and the patient is being monitored closely, bolus doses and increases in the drip rate can occur easily when more sedation is needed. Answer D is incorrect because there are changes as described.

4. Answer: A

During ECMO, blood flow to the gastrointestinal tract is compromised, making the oral route of administration

inappropriate for medications, which eliminates warfarin and aspirin as appropriate (Answers B and D are incorrect); moreover, warfarin takes days to work, which is another reason not to use this agent in ECMO. Because there is an extremely fine line between clotting and bleeding in ECMO, an agent that can be easily titrated is best. Heparin is a continuous infusion that can be titrated easily, especially with bedside testing (Answer A is correct). Enoxaparin, which lasts for extensive periods, would not be appropriate in ECMO (Answer C is incorrect).

5. Answer: B

The patient has decreased cardiac function. Milrinone is an inotropic agent that increases cardiac output. The patient also has an increased SVR, which milrinone would lower slightly (Answer B is correct). Norepinephrine is mainly used for warm shock (Answer A is incorrect). Dopamine could be used in a patient with normal cardiac function and hypotension, but this would not be appropriate for this patient (Answer C is incorrect). Phenylephrine is an α_1 -agonist only, which would make the patient hypertensive but would not affect the cardiac function (Answer D is incorrect).

6. Answer: B

The acronym for medications that can be administered by an endotracheal tube is LEAN: lidocaine, epinephrine, atropine, and naloxone. These are the only medications that can be given endotracheally during pediatric cardiac arrest (Answer B is correct). Amiodarone (Answer C), calcium (Answer A), and vasopressin (Answer D) are not given during pediatric cardiac arrest. Alternative acronym is NAVEL LANE. NAVEL (adults) and LANE (pediatrics).

7. Answer: D

Answer D, rapid intravenous push followed by rapid saline using a double-barrel technique, is correct. Although Answer A is technically rapid intravenous push, it is too slow. Answer B is incorrect because of the 30-minute duration, and no dilution is needed with adenosine. Answer C is incorrect because even though the drug is rapid intravenous push, the flush must also be rapid intravenous push to get all the medication into circulation.

8. Answer: C

This patient is in VF. The standard sequence of treatments for VF is as follows: shock, CPR, shock, CPR, epinephrine every 3–5 minutes, shock, and then amiodarone. Chances are that after the first shock, epinephrine would have been initiated if intravenous access had been obtained. Depending on when the third shock came, many doses of epinephrine would have been given. The next step in the sequence is amiodarone (Answer C is correct). The other choices have no role in VF. Atropine is for bradycardia (Answer A is incorrect), adenosine is for SVT (Answer B is incorrect), and procainamide is not in the PALS guidelines for VF (Answer D is incorrect).

9. Answer: B

This patient has VT, probably caused by her rhabdomyoma interfering with normal conduction. She has a pulse but poor perfusion, making her extremely unstable. Cardioversion is the best option to quickly return her to a perfusing rhythm (Answer B is correct). After the patient becomes less symptomatic and if she is still in a wide tachycardia, amiodarone would be appropriate (Answer A is incorrect). Magnesium is inappropriate because she has a monomorphic tachycardia, and the rhythm is not torsades de pointes (Answer D is incorrect). Lidocaine is used in pulseless VT or VF (Answer C is incorrect).

10. Answer: D

The patient developed torsades de pointes after the initial attempt at cardioversion. Magnesium 50 mg/kg over 10–20 minutes (with a pulse) or as a bolus (without a pulse) intravenously/intraosseously is the treatment of choice for torsades de pointes (Answer D is correct). Answers A–C would not be appropriate for treating torsades de pointes.

11. Answer: B

Mannitol is an osmolar agent that also decreases blood viscosity. The onset of decreased blood viscosity is quick but does not last long (1 hour) (Answer B is correct). The effects on osmolarity take about 15–20 minutes but can last for 6 hours. (Answers C and D are incorrect). Answer A is incorrect because 6 hours is the duration of action as an osmolar agent.

12. Answer: C

The patient is being well treated for ICP management. Sedation is always an important consideration in ICP

management, but in this case, it is adequate. Mannitol scheduled every 6 hours will help reduce blood viscosity for a short while and will work as an osmolar agent. Hypertonic saline is at an appropriate dose and is optimized, given the osmolar and sodium limits (350 mOsm/L and 175 mEq/L, respectively) (Answer A is incorrect). If an increased ICP were to occur, an extra dose of mannitol would probably have no effect (Answer B is incorrect). Phenytoin, which has little effect on ICP, should be used as seizure prophylaxis, if indicated (Answer D is incorrect). Barbiturate-induced coma would be the next step for this patient (Answer C is correct).

13. Answer: C

Propranolol will decrease resting energy expenditure (Answer C is correct; Answer B is incorrect). Answer A is incorrect because propranolol is a β -blocker and will decrease heart rate. Propranolol has been shown to increase lean body mass in burn patients (Answer D is incorrect).

PICU II

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Learning Objectives

1. Classify primary and compensatory acid-base disorders when given pertinent patient details, including laboratory values.
2. Recognize clinical and biochemical differences between diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) and determine appropriate management for each disorder.
3. Define status epilepticus (SE) and describe appropriate strategies for escalation of SE treatment.
4. Outline the therapeutic options for and management of acute respiratory distress syndrome (ARDS) in children.
5. Develop appropriate strategies for prevention and empiric treatment of hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP).
6. Describe appropriate interventions related to prevention and treatment of various gastrointestinal mucosa disorders.

Abbreviations in This Chapter

ABG	Arterial blood gas
AED	Antiepileptic drug
ARDS	Acute respiratory distress syndrome
DKA	Diabetic ketoacidosis
GCSE	Generalized convulsive status epilepticus
HAP	Hospital-acquired pneumonia
HHS	Hyperglycemic hyperosmolar state
H ₂ RA	Histamine-2 receptor antagonist
MDR	Multidrug resistant
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NMB	Neuromuscular blockade
PARDS	Pediatric acute respiratory distress syndrome
PICU	Pediatric intensive care unit
PPI	Proton pump inhibitor
RSE	Refractory status epilepticus
SE	Status epilepticus
SRMD	Stress-related mucosal disease
UGIB	Upper gastrointestinal bleeding
VAP	Ventilator-associated pneumonia

Self-Assessment Questions

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

1. A.S. is a 3-year-old boy (weight 13 kg) admitted to the pediatric intensive care unit (PICU) for pneumonia. He is not currently receiving any form of positive pressure ventilation. His most recent arterial blood gas (ABG) is a pH of 7.48, with partial pressure of carbon dioxide (Pco₂) 30 mm Hg and serum bicarbonate (HCO₃⁻) 22 mEq/L. Which primary acid-base disorder is most consistent with A.S.'s laboratory data?
 - A. Metabolic acidosis.
 - B. Respiratory acidosis.
 - C. Metabolic alkalosis.
 - D. Respiratory alkalosis.

Questions 2–4 pertain to the following case.

T.N. is a 5-year-old girl (weight 20 kg) who is in the PICU for status epilepticus (SE). Seizures lasted about 15 minutes before cessation after two doses of benzodiazepines. Her current laboratory values include the following: sodium (Na) 137 mEq/L, potassium (K) 4.2 mEq/L, HCO₃⁻ 18 mEq/L, chloride (Cl) 100 mEq/L, blood urea nitrogen (BUN) 20 mg/dL, serum creatinine (SCr) 0.3 mg/dL, and lactate 6 mmol/L. Her ABG includes pH 7.3 and Pco₂ 30 mm Hg.

2. Which primary acid-base disorder is most consistent with T.N.'s laboratory and clinical data?
 - A. Metabolic acidosis.
 - B. Respiratory acidosis.
 - C. Metabolic alkalosis.
 - D. Respiratory alkalosis.
3. Which is the most likely cause of T.N.'s acid-base disorder?
 - A. Hypoxemia secondary to the seizure.
 - B. Hyperglycemia secondary to the seizure.
 - C. Renal dysfunction secondary to the seizure.
 - D. Lactic acidosis secondary to the seizure.

4. Which best represents the calculated anion gap for T.N.?
- 5.
 - 11.
 - 19.
 - 40.
5. S.S. is a 7-year-old girl (weight 20 kg) who has had polydipsia, polyuria, and nausea/vomiting for the past week. She has no significant medical history. On admission to the emergency department, her point-of-care blood glucose was 578 mg/dL. She has a Kussmaul breathing pattern and is slightly obtunded; she also has extremely dry mucous membranes and skin tenting but is normotensive for age and height. After receiving 100 mL of 0.9% normal saline, she is transferred to the PICU. While awaiting her chemistry results, which would be the best initial treatment for her?
- Obtain an ABG.
 - Resuscitate with additional 100 mL of 0.9% sodium chloride over 30 minutes.
 - Resuscitate with additional 100 mL of 0.9% sodium chloride plus 20 mEq/L of potassium chloride over 30 minutes.
 - Initiate continuous regular insulin at 0.1 unit/kg/hour intravenously.
6. D.K. is a 14-year-old male adolescent with no pertinent medical history. He presents to the emergency department obtunded and in hypovolemic shock. His serum glucose is 1210 mg/dL and HCO_3^- is 16 mEq/L. He is given a diagnosis of hyperglycemic hyperosmolar state (HHS). He receives 20 mL/kg of 0.9% sodium chloride, followed by fluid deficit therapy with 0.75% sodium chloride. Which best depicts the desired rate of glucose decline during the first several hours of fluid therapy?
- 75–100 mg/dL/hour.
 - 50–75 mg/dL/hour.
 - Greater than 100 mg/dL/hour.
 - Less than 50 mg/dL/hour.
7. L.T. is a 14-year-old male adolescent (weight 65 kg) with a history of seizure disorder. He was at a friend's house for the weekend and forgot his seizure medication of topiramate. After returning home, he develops a tonic-clonic seizure lasting about 5 minutes, according to his mother. She administered 15 mg of rectal diazepam and called emergency medical services. Diazepam initially resulted in cessation of seizure activity, but on PICU admission, he began seizing again. He has peripheral intravenous access. Which would be the best emergent initial therapy for generalized clonic SE in this patient?
- Another 5-mg dose of rectal diazepam.
 - Lorazepam 4 mg intravenously.
 - Phenobarbital 1300 mg intravenously.
 - Midazolam continuous infusion at 0.1 mg/kg/hour.
8. R.M. is a 7-month-old boy (weight 8 kg) admitted to the PICU for new-onset GCSE. He has no pertinent birth or medical history. He has a social history of two sisters in day care and a dog and a cat. He presented to the PICU seizing which had been ongoing for 10 minutes. He was given two doses of lorazepam 0.8 mg intravenously, but they did not stop the seizures. Which would be the next best option for this patient?
- Diazepam 1 mg rectally.
 - Phenytoin 160 mg intravenously over 2 minutes.
 - Fosphenytoin 160 mg phenytoin equivalents (PE) intravenously over 6 minutes.
 - Valproic acid 320 mg intravenously over 10 minutes.
9. T.K. is a 5-year-old girl (weight 20 kg) with a history of recurrent otitis media who presented to the PICU 2 days earlier with community-acquired pneumonia and respiratory failure. Her respiratory status continues to worsen, and she is given a diagnosis of acute respiratory distress syndrome (ARDS). She is currently intubated on fraction of inspired oxygen (FiO_2) 0.8 (80% O_2) and positive end-expiratory pressure (PEEP) 12 cm H_2O . Despite optimizing her midazolam and fentanyl infusions and bolus doses, she continues to be hypoxemic. Echocardiography (ECHO) reveals no signs of right ventricular dysfunction. Which would be the best medication therapy for this patient?

- A. Methylprednisolone 20 mg intravenously every 6 hours.
- B. Lorazepam 4 mg intravenously every 6 hours as needed for agitation.
- C. Rocuronium infusion initiated at 0.6 mg/kg/hour.
- D. Inhaled nitric oxide at 20 ppm.
10. R.M. is a 14-month-old girl (weight 11 kg) admitted to the PICU and intubated for mechanical ventilation 72 hours earlier for respiratory failure and acute mental status changes. She has a medical history of autism, bronchopulmonary dysplasia, and gastroesophageal reflux disease. She is receiving famotidine for stress-related mucosal disease (SRMD) prophylaxis, midazolam 0.2 mg/kg/hour, and fentanyl 2 mcg/kg/hour. She has two peripheral intravenous lines and a Foley catheter. Currently, the head of the bed is elevated to 35 degrees, and she is receiving oral care with chlorhexidine. The hospital infection control supervisor is reviewing R.M. for her risk of ventilator-associated pneumonia (VAP). Which other prevention strategy would be best for this patient?
- A. Daily sedation holidays with assessment of extubation readiness.
- B. Discontinuation of SRMD prophylaxis.
- C. Venous thromboembolism prophylaxis with enoxaparin.
- D. Proton pump inhibitor (PPI) for SRMD prophylaxis.
11. A.P. is a 6-week-old girl (weight 3.5 kg) who was admitted to the PICU 16 days for group B *Streptococcus* sepsis, has now completed a course of therapy for this infection. She is receiving mechanical ventilation for respiratory failure. Overnight, her O₂ saturation worsened, decreasing to 88%, and she has developed an increase in respiratory secretions according to the respiratory therapist. Her morning complete blood cell count (CBC) includes a white blood cell (count) (WBC) of 3×10^3 cells/mm³ (78 polymorphonuclear leukocytes, 12 band neutrophils, 9 lymphocytes, and 3 monocytes), hemoglobin (Hgb) of 9 g/dL, hematocrit (Hct) of 30%, and platelet count of 100,000/mm³.
- Her vital signs include temperature 97°F, heart rate 180 beats/minute, respiratory rate 24 breaths/minute, and blood pressure 100/60 mm Hg. Her chest radiograph reveals new infiltrates. A mini-BAL (bronchoalveolar lavage) is sent, and antibiotics are initiated. Which antibiotic regimen would provide the best empiric coverage for this patient?
- A. Ampicillin/sulbactam 50 mg/kg/dose (of ampicillin component) every 6 hours plus gentamicin 5 mg/kg/dose intravenously every 24 hours plus vancomycin 15 mg/kg/dose every 6 hours.
- B. Ampicillin 100 mg/kg/dose every 6 hours plus gentamicin 5 mg/kg/dose intravenously every 24 hours plus vancomycin 15 mg/kg/dose every 6 hours.
- C. Cefepime 50 mg/kg/dose intravenously every 8 hours plus gentamicin 5 mg/kg/dose intravenously every 24 hours plus vancomycin 15 mg/kg/dose every 6 hours.
- D. Ceftriaxone 50 mg/kg intravenously every 24 hours plus gentamicin 5 mg/kg/dose every 24 hours plus vancomycin 15 mg/kg/dose every 6 hours.
12. N.M. is a 3-month-old African American boy (height 24 inches [61 cm], weight 4 kg) admitted to the PICU for dehydration and sepsis. He was born full term and has no significant birth or medical history. He was electively intubated in the PICU 2 days earlier because of altered mental status. He is currently receiving milrinone 0.25 mcg/kg/minute, midazolam 0.1 mg/kg/hour, and fentanyl 1 mcg/kg/hour. His most recent laboratory values include the following: Na 140 mEq/L, K 3.5 mEq/L, Cl 105 mEq/L, HCO₃⁻ 22 mEq/L, BUN 20 mg/dL, SCr 0.7 mg/dL, glucose 90 mg/dL, and international normalized ratio (INR) 1.82. Which would best for prevention of bleeding from SRMD in this patient?
- A. Famotidine 4 mg intravenously every 12 hours.
- B. Lansoprazole 4 mg by nasogastric tube daily.
- C. Sucralfate 5 mL by nasogastric tube every 6 hours.
- D. No stress ulcer prophylaxis needed.
13. S.R. is a 10-year-old girl (weight 25 kg) who has been in the PICU for more than 2 weeks. Her medical

history includes premature birth at 30 weeks' gestation, retinopathy of prematurity, laryngomalacia, cerebral palsy, developmental delay, and decreased gastrointestinal (GI) motility. She remains intubated and mechanically ventilated. During this admission, she has been treated for septic shock and has required an endoscopic intervention for an upper gastrointestinal bleed (UGIB). Which of S.R.'s risk factors has most consistently been identified as an independent risk factor for UGIB?

- A. Born prematurely.
- B. Respiratory failure.
- C. Previous GI bleed.
- D. Septic shock.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.2,1.3,1.4,1.5
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.5
3. Domain 3: Information Management, Research, and Education; Task(s): 3.2, 3.4

I. ACID-BASE DISORDERS

A. Background

1. Acid-base disorders are common in the PICU.
2. Evaluate for the primary disorder and the compensatory mechanism.
3. Assessment of primary disorder includes:
 - a. Blood gas (arterial preferred)
 - b. Serum chemistry
 - c. Detailed history
 - d. Medication review

B. Classification of Acid-Base Disorders

1. ABG assessment
 - a. pH
 - i. Negative log of $[H^+]$
 - ii. Regulated between 7.35–7.45
 - b. P_{CO_2}
 - i. Respiratory acid
 - ii. The rate and depth of ventilation vary to allow for excretion or retention of carbon dioxide (CO_2).
 - (a) Hyperventilation – Results in CO_2 elimination (decreasing P_{CO_2})
 - (b) Hypoventilation – Results in CO_2 retention (increasing P_{CO_2})
 - c. Capillary or venous blood source may be used with additional considerations.
2. Chemistry assessment
 - a. HCO_3^-
 - i. Metabolic base and most abundant extracellular buffer
 - ii. HCO_3^- excretion or retention regulated by kidneys
 - b. Calculate anion gap to help determine cause of derangement.
 - i. Anion gap = $Na^+ - (Cl^- + HCO_3^-)$. Some references may include potassium.
 - ii. Quantifies relationship between measured cations and anions to unmeasured ions
 - iii. Normal: 8–16 mEq/L (or 12–20 mEq/L when including K^+)
 - iv. Hypoalbuminemia may result in a falsely low anion gap.
 - c. Presence of lactate

Table 1. Arterial Blood Gas Values for Acid-Base Evaluation

	Normal Ranges
pH	7.35–7.45
P_{CO_2}	35–45 mm Hg
HCO_3^-	22–28 mEq/L

HCO_3^- = bicarbonate; P_{CO_2} = partial pressure of carbon dioxide.

3. Using blood gas and serum chemistry:
 - a. Identify acidosis or alkalosis on the basis of arterial pH.
 - b. Determine the primary disturbance and compensatory response on the basis of HCO_3^- and/or P_{CO_2} .
 - i. Respiratory compensation
 - (a) Rate and depth of ventilation are altered to eliminate or retain P_{CO_2} to return the pH to within the usual range.
 - (b) Occurs within minutes

- ii. Metabolic compensation
- Kidneys alter HCO_3^- retention or elimination to return pH to within the usual range.
 - Compensation takes 24–48 hours.

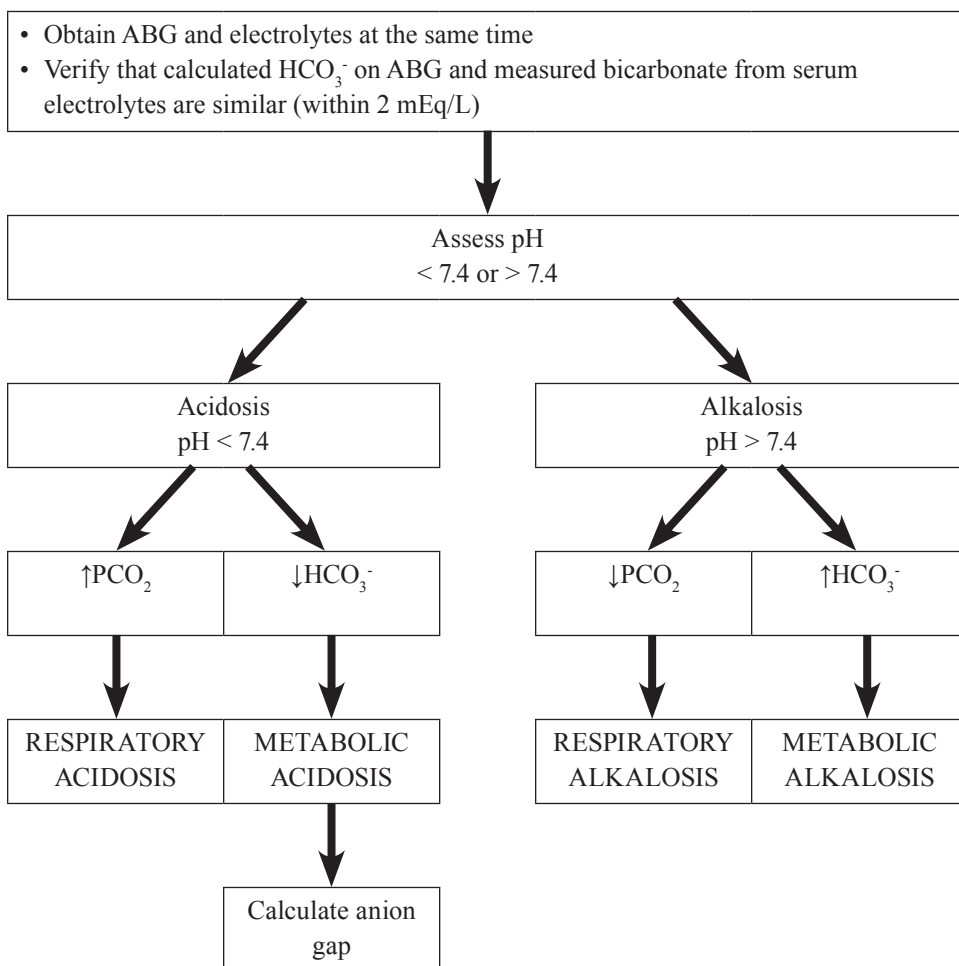


Figure 1. Algorithm for classifying acid-base disorders.

ABG = arterial blood gas; HCO_3^- = bicarbonate.

Table 2. Acid-Base Disturbances

Disorder	pH	Primary Disturbance	Compensatory Response
Metabolic acidosis	↓	↓ HCO_3^-	↓ Pco_2
Metabolic alkalosis	↑	↑ HCO_3^-	↑ Pco_2
Respiratory acidosis	↓	↑ Pco_2	↑ HCO_3^-
Respiratory alkalosis	↑	↓ Pco_2	↓ HCO_3^-

Table 3. Signs and Symptoms of Acidosis

Metabolic	Respiratory
Confusion/lethargy Flushing Hyperkalemia – Caused by extracellular shift Hyperventilation and/or Kussmaul breathing Nausea/vomiting Tachycardia Wide pulse pressures	Abnormal reflexes Altered mental status Coma Headache Papilledema Seizures

Table 4. Signs and Symptoms of Alkalosis

Metabolic	Respiratory
Altered mental status Cardiac arrhythmias Dizziness Hypokalemia – Caused by intracellular shift Muscle weakness/cramping Paresthesia	Altered mental status Cardiac arrhythmias Hypokalemia Nausea/vomiting Seizures Syncope

C. Management requires identification and treatment of both underlying cause and potentially life-threatening symptoms.

1. Common causes of metabolic acidosis may be found in Table 5.

Table 5. Common Causes of Metabolic Acidosis and Alkalosis

Metabolic Acidosis – Elevated Anion Gap	Metabolic Acidosis – Normal Anion Gap (Hyperchloremic Acidosis)
Mnemonic device “MUDPILES” is common Methanol, metformin Uremia Diabetic or starvation ketoacidosis Paraldehyde, propylene glycol Iron, isoniazid, ibuprofen, inborn errors Lactic acid Ethylene glycol, ethanol Salicylic acid	HCO ₃ ⁻ losses from GI tract (e.g., diarrhea, fistula) Renal tubular acidosis (RTA) types I, II, and IV • Cyclosporine • Topiramate • Spironolactone • Sulfamethoxazole/trimethoprim Hypoaldosteronism Other drugs (non-RTA mechanism) • Normal saline – rapid infusion/resuscitation • Acetazolamide • Chloride supplementation/replacement • Excessive magnesium intake
Metabolic Alkalosis – Chloride Responsive	Metabolic Alkalosis – Chloride Resistant
Vomiting Nasogastric suctioning Diuretic use Cystic fibrosis Laxative abuse Volume contraction	Hypoaldosteronism Exogenous mineralocorticoids Hypokalemia Refeeding syndrome Genetic conditions (e.g., Bartter or Gitelman syndrome)

Note: Excessive HCO₃⁻ or citrate administration, including in massive transfusion, may cause metabolic alkalosis. In patients with liver failure, citrate toxicity may alternatively cause elevated anion gap acidosis.

2. Management of metabolic acidosis
 - a. Removal of the offending agent
 - b. Administration of antidote, when available
 - c. Fluid administration
 - d. Hemodialysis
 - e. Provide supportive care through a period of toxin clearance.
 - f. Base administration can be considered to temper the adverse consequences of severe acidosis (pH of 7.1 or less).
 - i. Correct only to a pH of 7.2 to prevent overcorrection.
 - ii. Sodium bicarbonate dose:
 - (a) $[\text{desired HCO}_3^- (\text{mEq/L}) - \text{actual HCO}_3^- (\text{mEq/L})] \times \text{wt (kg)} \times 0.5 (\text{L/kg}) = \text{mEq of HCO}_3^-$ replacement. To prevent overcorrection, recommend not to use a desired HCO_3^- greater than 10–12 mEq/L.
 - (b) In clinical practice, doses of 0.5–1 mEq/kg up to a maximum of 50 mEq are often administered. Although this is an acceptable alternative and a more user-friendly calculation, care must be taken not to overcorrect the acidosis.
 - (c) Assess the response to sodium bicarbonate 30 minutes after administration.
 - iii. Risks with sodium bicarbonate administration
 - (a) Hypernatremia
 - (b) Hyperosmolality
 - (c) Worsening of intracellular acidosis
 - (d) Intracranial hemorrhage (increased risk in neonates)
 - (e) Myocardial injury
 - (f) Overcorrection (resulting in alkalosis or paradoxical CSF acidosis)
 - (g) Common intravenous incompatibilities and drug interactions
 - (1) Of note, some evidence suggests that alkaline solutions inactivate concurrently administered catecholamines.
3. Common causes of metabolic alkalosis may be found in Table 5.
4. Management of metabolic alkalosis: Chloride-responsive disorders can be managed by:
 - a. Minimizing chloride losses
 - i. Antiemetics
 - ii. Gastric acid suppression when nasogastric suctioning is required
 - iii. Reduction in diuretic doses
 - iv. Acetazolamide
 - b. Replacing chloride when losses cannot be minimized
 - i. Chloride can usually be replaced with sodium, potassium, and calcium chloride salts.
 - ii. Ammonium chloride: Ammonium is converted to ammonia, a base; excessive administration can result in worsening alkalosis.
 - iii. Arginine hydrochloride (0.475 mEq/mL)
 - (a) Dose may be calculated using HCO_3^- or chloride.
 - (1) $[\text{actual HCO}_3^- (\text{mEq/L}) - 24 \text{ mEq/L}] \times \text{wt (kg)} \times 0.5 (\text{L/kg}) = \text{mEq of arginine hydrochloride}$
 - (2) $[103 \text{ mEq/L} - \text{actual Cl}^- (\text{mEq/L})] \times \text{wt (kg)} \times 0.2 (\text{L/kg}) = \text{mEq of arginine hydrochloride}$
 - (b) In general, administer about half the calculated replacement dose before reassessment.
 - (1) Overdosage may result in hyperkalemia, metabolic acidosis, or cerebral edema.
 - (c) Arginine extravasation has caused severe skin necrosis requiring surgical intervention.
 - iv. When chloride replacement is insufficient or contraindicated, consider adding acetazolamide.

5. Common causes of respiratory acidosis and respiratory alkalosis can be found in Table 6.

Table 6. Common Causes of Respiratory Acidosis and Alkalosis

Respiratory Acidosis
Hypoventilation secondary to CNS depression • Ingestion (e.g., benzodiazepines, opioids, barbiturates) • Head injury • CNS infection • Stroke Hypoventilation secondary to neuromuscular disorders • Spinal cord injury • Guillain-Barré syndrome • Organophosphate poisoning Hypoventilation secondary to lung disease • Intrinsic/parenchymal disease (e.g., pneumonia, pulmonary edema, ARDS) • Upper airway obstruction (e.g., croup, foreign body aspiration) • Lower airway obstruction (e.g., status asthmaticus, bronchiolitis, chronic lung disease) • Massive PE • Pneumothorax
Respiratory Alkalosis
CNS disorders • Meningitis/encephalitis • Head trauma • Tumor • Severe anxiety Medications • Salicylates • Nicotine • Xanthine derivatives • Catecholamines Metabolic etiology • Sepsis • Hyperammonemia • Hyperthermia Hypoxemia secondary to pulmonary source (e.g., pneumonia, asthma, PE, pulmonary edema)

ARDS = acute respiratory distress syndrome; CNS = central nervous system; PE = pulmonary embolism

6. Management of respiratory disorders of acid-base: Because of the prolonged time to compensation by the renal system, respiratory disorders often require management by ventilation, either invasive or noninvasive positive pressure, while the underlying cause is corrected.

- D. Mixed disorders can occur and require a multipronged approach to determine the etiology and management.
1. In addition, two primary metabolic disorders can exist concurrently. However, two primary respiratory disorders cannot exist at the same time.
 2. Examples of common mixed disorders include
 - a. Respiratory acidosis and metabolic acidosis
 - i. Cardiac arrest
 - ii. Patients with chronic lung disease who present with shock

- b. Respiratory alkalosis and metabolic alkalosis
 - i. Mechanical ventilation and vomiting/nasogastric suctioning
 - ii. Mechanical ventilation and blood transfusions
 - c. Metabolic acidosis and respiratory alkalosis
 - i. Advanced liver disease
 - ii. Salicylate toxicity
 - iii. Pulmonary-renal syndromes
 - d. Metabolic alkalosis and respiratory acidosis
 - i. Chronic obstructive lung diseases and salt restriction/diuretics
 - ii. Chronic obstructive lung diseases and glucocorticoids
3. Treating these disorders consists of management of the underlying causes and symptomatic management of each disorder, when necessary.

II. DIABETIC KETOACIDOSIS AND HYPERGLYCEMIC HYPEROSMOLAR STATE

A. Diabetic Ketoacidosis (DKA)

1. Incidence varies by geographic location and is associated with the incidence of type 1 diabetes.
 - a. Frequency: 15%–70%
 - b. DKA as the presentation of new-onset diabetes mellitus is more common in:
 - i. Those younger than 5 years
 - ii. Those lacking readily accessible health care because of social or economic barriers
 - c. Occurrence in patients with a previous diabetes diagnosis is most commonly due to insulin omission.
 - i. Psychosocial factors contributing to intentional omission should be examined with each DKA admission.
 - d. Medications including high-dose corticosteroids, atypical antipsychotics, diazoxide, and immunosuppressive agents have been implicated in precipitation of DKA.
2. Mortality is rare and has decreased in response to advances in diabetes education and DKA management.
3. Pathophysiology
 - a. Relative or absolute insulin deficiency and increased production of counterregulatory hormones (e.g., glucagon, cortisol)
 - b. Resulting in:
 - i. Increased catabolism, increased glucose production, and impaired glucose use leading to hyperglycemia and hyperosmolality
 - ii. Lipolysis and ketogenesis leading to metabolic acidosis
 - iii. Osmotic diuresis, precipitating dehydration, renal dysfunction, and electrolyte loss
4. Biochemical criteria of diagnosis:
 - a. Hyperglycemia greater than 200 mg/dL (11 mmol/L)
 - b. Acidosis: pH less than 7.3 *or* HCO_3^- less than 15 mEq/L
 - c. Presence of ketones in the urine or serum.
 - i. When available, serum β -hydroxybutyrate should be measured; concentrations 3 mmol/L or greater are consistent with DKA.
5. Severity is used to characterize the degree of acidosis on presentation.
 - a. Mild: Venous pH less than 7.3 or HCO_3^- less than 15 mEq/L
 - b. Moderate: pH less than 7.2 or HCO_3^- less than 10 mEq/L
 - c. Severe: pH less than 7.1 or HCO_3^- less than 5 mEq/L
6. Clinical signs of DKA
 - a. Dehydration – Assess for the clinical severity of dehydration.
 - i. Clinical assessment can be impaired because of the hyperosmolar state.

- ii. 5% dehydration – Prolonged capillary refill time (greater than 2 seconds), reduced skin turgor, dry mucous membranes, lack of tears
 - iii. Greater than 10% dehydration – Weak peripheral pulses, hypotension, shock, oliguria
 - b. Tachycardia
 - c. Tachypnea
 - d. Kussmaul respirations with acetone-smelling breath
 - e. GI symptoms – Nausea, vomiting, and abdominal pain
 - f. Altered mental status
 - g. Of note, hypertension has been shown to occur in many children with DKA (despite hypovolemia).
 - i. Associated factors include greater severity of acidosis, lower Pco₂, and lower Glasgow Coma Scale scores, suggesting a centrally mediated cause.
 - ii. Appropriate volume replacement should still occur (see the text that follows), with close monitoring.
7. Laboratory assessment
 - a. Serum chemistries:
 - i. Glucose
 - ii. Sodium (must be corrected for elevated glucose value):
 - (a) If glucose measured in mg/dL, corrected sodium = measured sodium mEq/L + 2 x [(plasma glucose – 100)/100]
 - (b) If glucose measured in mmol/L, corrected sodium = measured sodium mEq/L + 2 x [(plasma glucose – 5.6)/5.6]
 - iii. Potassium – If measurement is delayed at presentation, obtain an electrocardiogram.
 - iv. HCO₃⁻
 - v. Phosphorus
 - vi. BUN/creatinine
 - vii. Anion gap (see Acid-Base section for calculation)
 - b. Effective osmolality = [2 x plasma sodium (mEq/L)] + [plasma glucose (mg/dL)/18]
 - i. If glucose is in mmol/L, do not divide by 18.
 - c. Venous pH and Pco₂
 - d. CBC – Of note, elevated WBC is a common DKA stress response and may not be suggestive of infection.
 - e. Assessment of ketosis via urinalysis and/or β-hydroxybutyrate
 - f. Hemoglobin A1c
8. Fluid and electrolyte therapy
 - a. Goals:
 - i. Restore circulating plasma volume.
 - ii. Replace sodium and total body water deficits.
 - iii. Correct electrolyte abnormalities – Hypokalemia and potentially hypophosphatemia
 - iv. Enhance glucose and ketone clearance through maintaining or improving glomerular filtration.
 - b. Resuscitation
 - i. 10 mL/kg of 0.9% sodium chloride intravenously over 30–60 minutes
 - (a) May be repeated with second fluid bolus if tissue perfusion remains inadequate
 - ii. In the patient presenting with shock, administer 20 mL/kg rapidly to restore circulatory volume, and reassess after each bolus.
 - iii. Resuscitation phase of fluid replacement may not be necessary for mild DKA.
 - c. Deficit replacement
 - i. Volume requirement
 - (a) Most patients present with a 5%–10% fluid deficit.
 - (b) Replace estimated fluid deficit at steady rate over 24–48 hours.

- (c) Provide deficit plus usual daily maintenance.
 - (d) Fluid rates rarely exceed 1.5–2 times the maintenance fluids.
 - ii. Sodium content/fluid tonicity
 - (a) Use isotonic solutions (0.9% sodium chloride, Ringer lactate, or Plasmalyte) for the initial 4–6 hours; then may consider transition to fluid with a tonicity of 0.45% sodium chloride or greater
 - (b) Decision to change to hypotonic fluid is based on hydration status, corrected sodium concentration, and serum osmolality.
 - (c) No difference in neurologic outcomes has been observed when fluids with a tonicity of 0.45% sodium chloride are used for the initial deficit replacement compared with isotonic saline.
 - iii. Addition of dextrose
 - (a) Dextrose is added to fluids to allow sufficient insulin delivery to reverse acidosis.
 - (b) 5% dextrose should be added to fluid therapy once the serum glucose concentration reaches 250–300 mg/dL or sooner if the glucose decreases by more than 90 mg/dL/hour.
 - iv. Potassium replacement
 - (a) Patients typically present with a total body potassium deficit from intracellular losses secondary to an extracellular shift from hypertonicity.
 - (1) Usual deficit: 3–6 mEq/kg
 - (b) Except in renal failure, potassium replacement is required because of several factors:
 - (1) Serum potassium decrease subsequent to volume expansion
 - (2) Intracellular shift secondary to insulin therapy
 - (3) Urinary losses resulting from aldosterone-like effect of insulin on the renal tubule
 - (c) Replacement generally begins at onset of fluid deficit replacement and insulin therapy and should continue throughout fluid therapy.
 - (d) With hypokalemia on presentation, potassium should be initiated prior to insulin initiation.
 - (1) For profound hypokalemia (potassium less than 2.5 mEq/L), insulin should be delayed until potassium is corrected to reduce the risk of cardiopulmonary compromise.
 - (e) Usual concentration: 20–40 mEq/L as combination of chloride, acetate, and/or phosphate
 - (f) Potassium administration typically should not exceed 0.5 mEq/kg/hour.
 - v. Phosphate replacement
 - (a) Intracellular phosphorus is depleted secondary to osmotic diuresis and may be exacerbated by insulin-related intracellular shift.
 - (b) Symptomatic hypophosphatemia (e.g., encephalopathy, impaired myocardial contractility, respiratory failure from respiratory muscle weakness) or severe asymptomatic hypophosphatemia (e.g., phosphate less than 0.4 mmol/L) should be treated with phosphorus replacement.
 - (1) Phosphate repletion for mild to moderate hypophosphatemia may be considered; clinical benefit of this practice is unclear.
 - (2) Hypophosphatemia may progress to clinically significant severity if intravenous insulin therapy continues beyond 24 hours without resumption of enteral dietary intake.
 - (c) Phosphate salt of potassium may be used as a portion of the potassium replacement in fluid therapy to minimize chloride load and prevent exacerbation of hypophosphatemia secondary to insulin therapy.
 - (d) Phosphate salts are generally ordered in millimoles, whereas potassium is often dosed in milliequivalents, which can lead to errors. 3 mmol of phosphate = 4.4 mEq of potassium
 - vi. Administration considerations
 - (a) Because of the rate of metabolic changes and frequency of laboratory monitoring, fluids are often adjusted during the deficit replacement phase of DKA management.

- (b) Fluids can be managed using either a one- or a two-bag system.
- (c) The two-bag system consists of two bags with different dextrose concentrations and generally, though not always, identical electrolyte components. Thus, adjusting the rate of the individual fluids adjusts the glucose infusion rate (Figure 2).
- (d) Potential benefits of the two-bag system include faster fluid change rate, fewer intravenous fluid bags used, reduced cost, and faster rate of HCO_3^- and ketone correction.
- (e) Standardization may reduce risk of compounding errors.

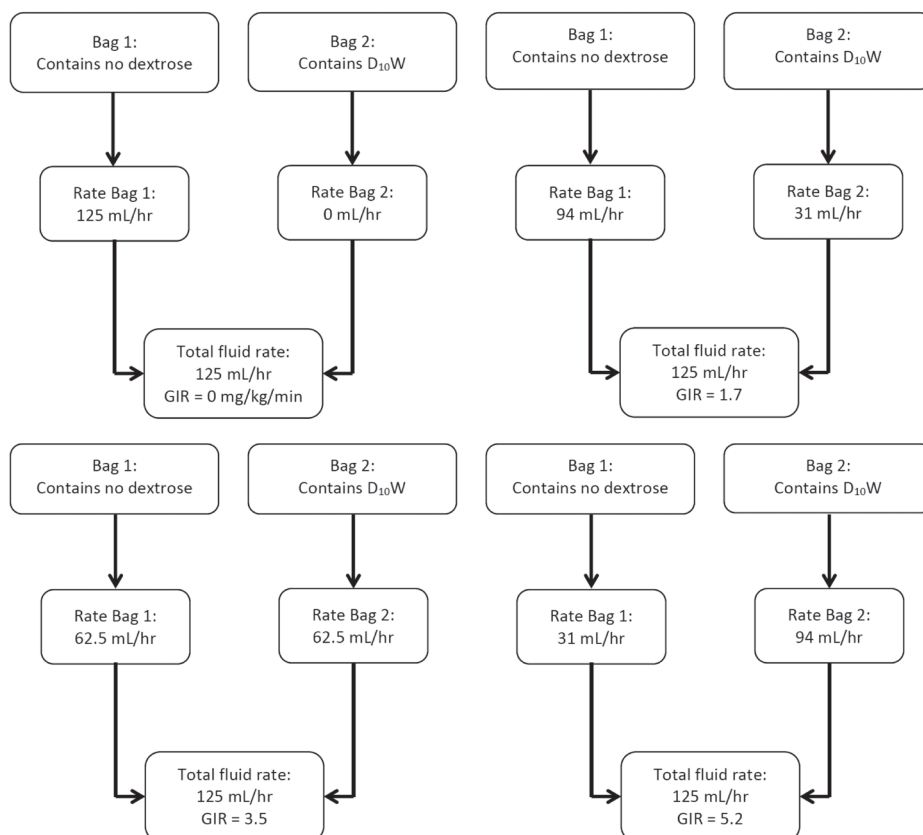


Figure 2. Example of using the two-bag method of fluid deficit replacement to modify the glucose infusion rate for a 30-kg patient with diabetic ketoacidosis presenting with a 10% fluid deficit. Bag 1 = 0.9% sodium chloride plus potassium chloride 20 mEq/L plus potassium phosphate 20 mmol/L. Bag 2 = 10% dextrose in water (D₁₀W)/0.9% sodium chloride plus potassium chloride 20 mEq/L plus potassium phosphate 20 mmol/L. Of note: Bag 2 can be made with a different tonicity of sodium chloride, or both bags can contain the same tonicity of sodium chloride, as shown in the example. In addition, Ringer lactate could be used to replace sodium chloride in one or both bags.

GIR = glucose infusion rate.

9. Insulin administration

- a. Acidosis in DKA is generally secondary to the insulin deficiency.
- b. Goals of therapy:
 - i. Normalize cellular metabolism.
 - ii. Normalize blood glucose.
 - iii. Reverse acidosis through suppression of lipolysis and ketogenesis.
- c. Begins 1–2 hours after fluid initiation

- d. Regular insulin at 0.05–0.1 unit/kg/hour
 - i. Do NOT give a bolus of insulin at therapy initiation.
 - (a) Bolus dosing may increase the risk of cerebral edema and can exacerbate hypokalemia.
 - ii. No difference in efficacy or safety between 0.05 and 0.1 unit/kg/hour infusion rates has been noted to date.
 - iii. Target rate of serum glucose decrease: 50 mg/dL/hour – Not to exceed 100 mg/dL/hour.
 - iv. If the serum glucose decrease is greater than 100 mg/dL/hour:
 - (a) Increase the glucose infusion rate of intravenous fluids.
 - (1) 10%–12.5% dextrose may be needed to maintain serum glucose or minimize the rate of decrease in serum glucose in patients for whom decreasing insulin is not reasonable.
 - (b) If metabolic acidosis continues to resolve, decrease the insulin infusion rate, generally not to less than 0.03 unit/kg/hour, in patients with marked sensitivity to insulin, including:
 - (1) Younger patients
 - (2) Older patients with established diabetes
- 10. Sodium bicarbonate
 - a. Acidosis correction with HCO_3^- has no clinical benefit and can have significant consequences in patients with DKA, including:
 - i. Paradoxical CNS acidosis
 - ii. Hypokalemia from rapid acidosis correction
 - iii. Increasing osmolality from additional sodium administration
 - b. Judicious, cautious acidosis correction with sodium bicarbonate may be considered for the following indications in patients with DKA:
 - i. Life-threatening hyperkalemia
 - ii. Severe acidosis (pH less than 6.9) with impaired cardiac contractility
 - c. If needed, administer no more than 2 mEq/kg over 60 minutes.
- 11. Managing complications from DKA and associated therapies
 - a. Cerebral edema
 - i. Although mortality from DKA is rare, 60%–90% of mortality is secondary to cerebral edema.
 - ii. Mental status changes and evidence of cerebral edema may present in around 15% of patients with DKA, but clinically overt cerebral edema is uncommon.
 - iii. The cause of cerebral edema and clinical overt edema is not well defined.
 - iv. Potential risk factors:
 - (a) Younger age
 - (b) New onset diabetes mellitus
 - (c) Longer duration of symptoms before presentation
 - (d) Sodium bicarbonate therapy
 - (e) Greater volume of fluid in first 4 hours
 - (f) Insulin initiation during the first hour of fluid therapy
 - (g) Metabolic abnormalities at presentation:
 - (1) Degree of hypocapnia after adjustment for acidosis
 - (2) Increased BUN
 - (3) Severity of acidosis
 - (h) Metabolic abnormalities once treatment is initiated:
 - (1) Marked decline in effective osmolality (evidence is mixed to date)
 - (2) Attenuated increase or early decrease in corrected serum sodium
 - v. Hyperosmolar therapy should be readily available within a secured area on the patient care unit. For a detailed discussion of hyperosmolar therapy, please see the PICU I chapter.

- b. Hyperchloremic metabolic acidosis can occur as a result of necessary isotonic fluid replacement volume.
 - i. Can result in misinterpretation of DKA resolution if base excess, HCO_3^- concentration, or anion gap is used to evaluate resolution.
 - ii. To ensure appropriate interpretation of resolution, β -hydroxybutyrate concentrations can be used in patients with hyperchloremia.
 - iii. Strategies to minimize hyperchloremia:
 - (a) Use potassium salts containing no more than 20 mEq/L of chloride
 - (b) Use Ringer lactate or Plasmalyte fluids.
 - iv. Hyperchloremic metabolic acidosis will resolve following discontinuation of fluid therapy.
 - c. Electrolyte abnormalities – Replace potassium, calcium, magnesium, and phosphorus as needed.
 - d. Venous thromboembolism – Avoid central venous catheter use when possible.
12. DKA resolution:
- a. Resolution of acidosis
 - i. HCO_3^- of 18 mEq/L or greater
 - ii. Venous pH greater than 7.3
 - iii. Normalization of β -hydroxybutyrate
 - (a) Occurs before resolution of ketone detection in urine.
 - (b) Can help discern whether persistent acidosis is the result of hyperchloremia
 - b. Glucose less than 200 mg/dL
 - c. Initiate subcutaneous insulin once enteral feeds and fluids are tolerated – See the Endocrinology/ Metabolic chapter for a detailed discussion of diabetes mellitus management.
 - i. To prevent rebound hyperglycemia, the first injection should be given 15–30 minutes (if rapid acting) or 1–2 hours (if regular insulin) before discontinuing infusion.

B. Hyperglycemic Hyperosmolar State (HHS)

1. Extreme elevations in serum glucose and osmolality without significant ketosis
2. May occur in both type 1 and type 2 diabetes
3. HHS remains considerably less common than DKA in pediatric patients.
4. Because of the more subtle signs and symptoms at presentation, HHS may go unrecognized.
 - a. Severe dehydration and electrolyte abnormalities may be present
 - b. Fluid deficit of 12%–15% of body weight is generally assumed
5. Biochemical criteria for diagnosis include:
 - a. Hyperglycemia greater than 600 mg/dL (33 mmol/L)
 - b. Normal or mild acidosis:
 - i. Moderate acidosis may occur in severe dehydration
 - c. Ketones
 - i. Urine – Small
 - ii. Serum – Small or absent
 - d. Effective serum osmolality greater than 320 mOsm/kg
 - e. Patient presents obtunded, combative, or with seizures.
6. Fluid and electrolyte management
 - a. Goals of therapy
 - i. Expand total body fluid.
 - ii. Restore renal perfusion.
 - iii. Promote a gradual decrease in corrected serum sodium and osmolality.
 - (a) Lack of decrease in corrected serum sodium is associated with mortality and is an indication for dialysis.

-
- iv. Replace urinary losses.
 - v. Decrease serum glucose.
 - (a) Decrease of 75–100 mg/dL/hour is expected in the first few hours with fluid therapy alone.
 - (b) Lack of decrease at expected rate should prompt an assessment of renal function.
 - b. Resuscitation fluids
 - i. Initial fluid bolus of 20 mL/kg or greater of 0.9% sodium chloride
 - ii. Infused over a much shorter duration than in DKA, though no specific rate is suggested
 - iii. Additional boluses should be given to restore peripheral perfusion.
 - c. Deficit replacement
 - i. Initiate 0.45%–0.75% sodium chloride to replete remaining fluid deficit over 24–48 hours.
 - ii. Utilize 0.9% sodium chloride in patients with poor perfusion or hemodynamic instability.
 - iii. Goal rate of serum sodium decline is 0.5 mEq/L per hour (12 mEq/L per day).
 - d. Addition of dextrose
 - i. If the rate of serum glucose decrease is greater than 90 mg/dL/hour after several hours of fluid replacement, dextrose may be added to fluids.
 - (a) Initial concentration: 2.5%–5%
 - e. Potassium replacement
 - i. Initiate potassium replacement once:
 - (a) Serum potassium concentrations within normal range
 - (b) Adequate renal function
 - ii. Include 40 mEq/L of potassium, with one-half as phosphate salt.
 - iii. Expect increased requirements once insulin is initiated.
 - f. Phosphorus replacement
 - i. Hypophosphatemia is generally more severe than in DKA.
 - ii. Goal of therapy: Avoid the adverse consequences of severe hypophosphatemia.
 - iii. Initiate with potassium replacement
 - 7. Insulin therapy
 - a. Acidosis from lactic acid may be present, but ketoacid production is low; therefore, early insulin therapy is not necessary.
 - b. Initiate intravenous insulin at rate of 0.025–0.05 units/kg/hour when fluid administration alone no longer causes rate of serum glucose decline of at least 50 mg/dL per hour.
 - i. Goal of therapy: Maintain a rate of serum glucose decline of 50–75 mg/dL per hour.
 - ii. Consider initiating sooner if the patient has moderate to severe ketosis.
 - 8. Sodium bicarbonate is contraindicated due to increased risk of life-threatening hypokalemia and negative impact on tissue O₂ delivery.
 - 9. Complications from HHS and associated therapies
 - a. Early insulin administration
 - i. Cardiovascular compromise and thrombosis may result from rapid decrease in serum glucose and osmolality in the absence of adequate fluid replacement
 - ii. Life-threatening hypokalemia
 - b. Venous thromboembolism
 - i. Avoid central venous catheter use when possible.
 - ii. Consider low-dose heparin infusion if requiring central venous catheters for more than 24–48 hours.
 - c. Rhabdomyolysis
 - d. Malignant hyperthermia
 - i. Cause is unknown; patients with increased temperature and risk in creatine kinase may benefit from dantrolene administration.
-

- e. Risk of cerebral edema is low, but a patient with altered mental status despite correction of osmolality should be evaluated for this condition.

Table 7. Comparison of DKA and HHS

	DKA	HHS
Serum glucose	> 200 mg/dL	> 600 mg/dL
Acidosis	Venous pH < 7.3 HCO_3^- < 15 mEq/L	Venous pH > 7.3 HCO_3^- > 15 mEq/L
Ketonemia	Present	Mild to absent
Fluid therapy	Resuscitation fluid: 10–20 mL/kg of isotonic crystalloid over 1–2 hr Deficit fluid: Initially, isotonic (4–6 hr); then can consider $\geq 0.45\%$ NaCl Add dextrose once serum glucose is 250–300 mg/dL – Initial concentration 5%	Resuscitation fluid: ≥ 20 mL/kg of 0.9% NaCl over < 1 hr Deficit fluid: Initially 0.45%–0.75% NaCl; increase [Na] to maintain perfusion/hemodynamics; adjust [Na] for gradual decline in serum sodium; add dextrose (2.5%–5%) to prevent decrease in serum glucose > 90 mg/dL/hr after first few hours of replacement fluids
Replacement of urinary losses	No	Yes
Insulin therapy	Bolus not recommended 0.05–0.1 unit/kg/hr Initiate after administration of resuscitation fluids completed (generally 1–2 hr after initiation of fluid therapy)	Bolus not recommended 0.025–0.05 unit/kg/hr Initiate when rate of serum glucose decrease is < 50 mg/dL/hr from fluid therapy alone
HCO_3^- therapy	May be considered in specific situations	Contraindicated

DKA = diabetic ketoacidosis; HHS = hyperglycemic hyperosmolar state; NaCl = sodium chloride.

Patient Case

1. B.L. is a 17-year-old male adolescent (weight 62 kg) with no pertinent medical history. He presents with serum glucose 885 mg/dL, venous pH 7.19, HCO_3^- 10 mEq/L, serum osmolality 325 mOsm/kg, and moderate ketones. He is pale with a moderately prolonged capillary refill time, but his peripheral pulses are good. His mental status is altered. Which is the best diagnosis and initial therapy?
 - A. HHS; administer 1250 mL of 0.9% sodium chloride over 1 hour, continuous insulin infusion 0.05 unit/kg/hour after completion of fluids.
 - B. DKA; administer 650 mL of 0.9% sodium chloride over 1 hour, continuous insulin infusion 0.05 units/kg/hour after completion of fluids.
 - C. HHS; administer 1250 mL of 0.9% sodium chloride over 10 minutes, regular insulin bolus 6 units.
 - D. DKA; administer 650 mL of 0.9% sodium chloride over 10 minutes, regular insulin bolus 6 units.

III. STATUS EPILEPTICUS

- A. SE refers to prolonged seizures or recurrent seizures without return of neurologic baseline.
- B. Life-Threatening Neurologic Emergency
- C. Definitions with varying seizure durations have been published to describe SE. The most recent definitions propose a much shorter seizure duration of 5 minutes or greater because:
 - 1. Most seizures last less than 5 minutes
 - 2. Those lasting longer are unlikely to spontaneously resolve
 - 3. Emergency treatment is vital
- D. Defining SE with a shorter seizure duration may result in the inclusion of some patients with prolonged seizures who would not traditionally meet the criteria for SE.
- E. Definitions and Classification of SE
 - 1. SE: Seizures that are continuous, either clinical or electrographic, or recurrent without recovery between, which last more than 5 minutes
 - 2. Generalized convulsive status epilepticus (GCSE)
 - a. Generalized tonic-clonic movements
 - b. Impaired mental status
 - c. Postictal period may consist of focal neurologic deficits.
 - 3. Nonconvulsive SE - electrographic seizure activity without associated clinical findings
 - 4. Refractory status epilepticus (RSE)
 - a. Patients with seizures unresponsive to standard treatment regimens
 - b. What constitutes failure to respond is controversial – Usually considered failure to respond to an adequate dose of benzodiazepine and one additional antiepileptic drug (AED)
- F. Patients should undergo a diagnostic workup to identify and evaluate the cause of SE.
 - 1. Etiology classification
 - a. Febrile: Associated with a febrile illness, non-CNS infection
 - b. Structural/metabolic: CNS infection, toxins, vascular, trauma, electrolyte abnormalities, inborn error of metabolism, chromosomal, tumor
 - c. Genetic
 - d. Unknown
 - 2. Laboratory workup
 - a. New-onset SE
 - i. Electrolytes and blood glucose
 - ii. Electroencephalogram (EEG)
 - iii. Computed tomography/magnetic resonance imaging (CT/MRI)
 - iv. With clinical suspicion: Urine drug screen, genetic/metabolic workup
 - v. In the febrile patient: CBC, lumbar puncture, additional cultures as appropriate
 - b. SE in a patient with a known seizure disorder
 - i. AED concentrations
 - ii. With clinical suspicion: Electrolytes, EEG, genetic workup, CT/MRI
 - iii. In the febrile patient: CBC, lumbar puncture, additional cultures as appropriate

- G. Medication Therapy – For a detailed discussion of AED therapy, please see the Neurology/Psychiatry chapter.
1. Treat the underlying cause – Resolve underlying metabolic abnormalities (e.g., hypoglycemia, sodium).
 2. Therapies are delineated as shown in Table 8.

Table 8. AED Therapies

Neurocritical Care Society Guideline	Time from Seizure Onset (min)	American Epilepsy Society Guideline	Time from Seizure Onset (min)
Emergent initial	0–5	Initial therapy phase	5–20
Urgent control	5–10	Second therapy phase	20–40
RSE	20–60 (after the second AED administered)	Third therapy phase	40–60

AED = antiepileptic drug; RSE = refractory status epilepticus.

- Emergent initial/initial therapy phase: Benzodiazepine is recommended by both the Neurocritical Care Society and the American Epilepsy Society guideline.
 - No significant differences between efficacy of intravenous benzodiazepines have been established.
 - Midazolam appears to be the most effective benzodiazepine when administered by a non-intravenous route in patients without access.
- Urgent control/second therapy phase
 - Seizures may continue in about 50% of pediatric patients after receiving benzodiazepines.
 - Choice of first agent is not well defined; fosphenytoin/phenytoin is historically most widely used, but mounting evidence (including recently published ESETT, ConSEPT, and EcLiPSE trials) suggests that levetiracetam and valproic acid have similar efficacy.

Table 9. Emergent Initial and Urgent Control Therapy for SE

Medication	Dosing	Route in SE: Administration Considerations	Place in Therapy	Clinical Pearls: Significant Adverse Effects
Diazepam	2–5 yr: 0.5 mg/kg 6–11 yr: 0.3 mg/kg ≥ 12 yr: 0.2 mg/kg Maximum single dose = 20 mg	Rectal	Emergent ^a Initial therapy ^b	Useful for out-of-hospital management and in those with no IV access Commercially available rectal gel formulations dosed in 2.5-mg increments Rapid redistribution results in shorter duration of effect Active metabolites Respiratory depression
	0.15–0.2 mg/kg Maximum single dose = 10 mg	IV Slow IV push Maximum rate = 2 mg/min		

Table 9. Emergent Initial and Urgent Control Therapy for SE (*continued*)

Medication	Dosing	Route in SE: Administration Considerations	Place in Therapy	Clinical Pearls: Significant Adverse Effects
Lorazepam	0.1 mg/kg Maximum single dose = 4 mg	IV Give IV push Maximum rate = 2 mg/min	Emergent ^a Initial therapy ^b	Generally considered the benzodiazepine of choice when IV access is available Dilute before administration to minimize injection-site pain IV formulation contains benzyl alcohol and propylene glycol Respiratory depression Hypotension
Midazolam	0.2 mg/kg Maximum single dose = 10 mg	Intramuscular	Emergent ^a Initial therapy ^b	Non-IV routes useful for out-of-hospital management and in those with no IV access For intranasal administration – Use of an atomizer is preferred For all non-IV routes, use more concentrated product to minimize administered volume Rapid redistribution results in shorter duration of effect Active metabolites Respiratory depression Hypotension (IV)
	0.2 mg/kg Maximum single dose = 10 mg	Intranasal Maximum 1 mL per nostril		
	0.5 mg/kg Maximum single dose = 10 mg	Buccal		
	Bolus: 0.2 mg/ kg Continuous infusion: Initiate at 0.1 mg/kg/hr	Continuous infusion	Urgent ^a Third phase ^b	
Fosphenytoin	20 mg PE/kg Maximum single dose = 1500 mg	IV Maximum rate: 3 mg PE/kg/min up to 150 mg PE/min Intramuscular	Emergent ^a Urgent ^a Second therapy ^b	Preferred to IV phenytoin because of tolerability May give an additional 5–10 mg PE/kg if seizure continues 10 min after dose Hypotension Arrhythmia
Phenytoin	20 mg/kg	IV Maximum rate: 1 mg/kg/min up to 50 mg/min	Emergent ^a Urgent ^a Second therapy ^b	May give an additional 5–10 mg/kg if seizure continues 10 min after dose IV formulation contains propylene glycol Hypotension Arrhythmia Injection-site pain/extravasation “Purple glove syndrome”

Table 9. Emergent Initial and Urgent Control Therapy for SE (*continued*)

Medication	Dosing	Route in SE: Administration Considerations	Place in Therapy	Clinical Pearls: Significant Adverse Effects
Phenobarbital	20 mg/kg	IV Maximum rate: 50 mg/min	Emergent ^a Urgent ^a Second therapy ^b	May give an additional 5–10 mg/kg if seizure continues 10 min after dose IV formulation contains propylene glycol Respiratory depression Hypotension
Levetiracetam	20–60 mg/kg Maximum single dose = 4500 mg	IV Maximum rate: 5 mg/kg/min	Emergent ^a Urgent ^a Second therapy ^b	Dose adjustment is recommended in renal dysfunction
Valproate sodium	20–40 mg/kg Maximum single dose = 3000 mg	IV Maximum rate: 3 mg/kg/min	Emergent ^a Urgent ^a Second therapy ^b	May be preferred agent for those with a history of generalized epilepsy Hepatotoxicity – Risk increased in patients < 2 yr Hyperammonemia Pancreatitis Thrombocytopenia
Pyridoxine	100 mg	IV	Urgent ^a	Consider in patients < 2 yr

^aNeurocritical Care Society guidelines.^bAmerican Epilepsy Society guidelines.

IV = intravenous(ly); PE = phenytoin sodium equivalents; SE = status epilepticus.

Table 10. Therapy for RSE According to the Neurocritical Care Society Guidelines

Medication	Dosing	Clinical Pearls Significant Adverse Reactions
Midazolam	Loading dose: 0.2 mg/kg Maximum = 10 mg Maintenance infusion: 0.1–1.5 mg/kg/hr	Use caution when evaluating dosing in the literature because of various units – mcg/kg/min and mg/kg/hr Infuse bolus dose at maximum rate of 2 mg/min For breakthrough seizures Bolus dose of 0.1–0.2 mg/kg Increase infusion by 0.05–0.1 mg/kg/hr every 3–4 hr Active metabolite may accumulate in renal dysfunction Tachyphylaxis with prolonged use Respiratory depression Hypotension
Pentobarbital	Loading dose: 5–15 mg/kg Maintenance infusion: 0.5–5 mg/kg/hr	Maximum infusion rate 50 mg/min For breakthrough seizures: Bolus doses of 5 mg/kg Increase infusion by 0.5–1 mg/kg/hr every 12 hr. Frequent titration of infusion dose can result in medication accumulation because of long elimination half-life IV formulation contains propylene glycol; monitor for toxicity with high doses or prolonged use Hypotension Respiratory depression Cardiac depression Paralytic ileus
Propofol	Loading dose: 1–2 mg/kg Maintenance infusion: 30–200 mcg/kg/min	Use caution when evaluating dosing in the literature because of differing units – mcg/kg/min and mg/kg/hr For breakthrough seizures: Increase infusion by 5–10 mcg/kg/min every 5 min Bolus dose of 1 mg/kg PLUS infusion increase Use caution with doses of > 65 mcg/kg/min (4 mg/kg/hr) or duration > 4 days Account for lipid calories (1.1 kcal/mL) in total daily calories Hypotension Respiratory depression Hypertriglyceridemia Propofol-related infusion syndrome; monitor for toxicity with high doses or prolonged use

Urgent control therapies that may also be considered for RSE: Fosphenytoin, lacosamide, levetiracetam, phenobarbital, phenytoin, topiramate, valproate sodium

- c. Treatment of RSE
 - i. Respiratory depression and failure occur with most RSE therapies; patients require a secure airway and mechanical ventilation.
 - ii. In pediatric patients, continuous infusion AED therapy is recommended for RSE.
 - iii. Once cessation of electrographic seizures or burst suppression is achieved, provide 24–48 hours of continuous infusion AED therapy before weaning.
 - iv. Add-on therapy with alternative agents such as lacosamide may also be considered.

Patient Case

2. J.R. is a 16-year-old female adolescent (weight 52 kg) with no known significant medical history. As reported by her track coach, she fell down during practice, and her left leg began shaking uncontrollably, followed by uncontrolled shaking of her entire body. The shaking stopped without intervention in about 5 minutes, but J.R. still could not be awakened. Her coach called 911, and J.R. was immediately transferred by ambulance to the hospital, where she was admitted to the PICU. On arrival to the PICU, she had another brief seizure that was treated with lorazepam. Her vital signs in the PICU included temperature 100.7°F, respiratory rate 20 breaths/minute, heart rate 128 beats/minute, and blood pressure 130/70 mm Hg. Significant laboratory values included Na 129 mEq/L, K 5.1 mEq/L, Cl 105 mEq/L, CO₂ 25 mEq/L, BUN 22 mg/dL, SCr 1.4 mg/dL, lactic acid 8 mg/dL, and albumin 2.5 g/dL. About an hour later, J.R. begins to seize again. Which is the best treatment option for this patient?
- A. Lorazepam 4 mg intravenously.
 - B. 0.9% sodium chloride at a rate of 50 mL/hour.
 - C. Phenobarbital 20 mg intravenously.
 - D. Propofol infusion at 1 mg/kg/hour.

IV. ACUTE RESPIRATORY DISTRESS SYNDROME

- A. Clinical syndrome of pulmonary edema of noncardiogenic origin secondary to damaged alveolarendothelial barrier
- B. Results in protein rich fluid accumulation in the alveoli
- C. This occurs at the same time as inflammatory dysregulation, inappropriate leukocyte and platelet activation, uncontrolled activation of coagulation, surfactant loss, and impaired lymphatic drainage.
- D. Combined, these result in the clinical signs of ARDS:
 - 1. Hypoxemia
 - 2. Chest radiographic findings
 - 3. Increased venous admixture
 - 4. Decrease in functional residual capacity of the lungs
 - 5. Increased dead space
 - 6. Decreased lung compliance
- E. Various criteria for defining pediatric ARDS (PARDS) have been set forth.
 - 1. Pediatric consensus statement addresses the potential insufficiencies in the Berlin definition when applied to a broad pediatric patient population and offers a definition for PARDS.

2. Knowledge of oxygenation metrics is needed to classify ARDS and PARDS.
 - a. PF ratio = $\text{PaO}_2/\text{FiO}_2$
 - b. SF ratio = peripheral capillary oxygen saturation (SpO_2)/ FiO_2
 - c. Oxygenation index = $(\text{FiO}_2 \times \text{mean airway pressure} \times 100)/\text{PaO}_2$
 - d. O_2 saturation index (OSI) = $(\text{FiO}_2 \times \text{mean airway pressure} \times 100)/\text{SpO}_2$
3. The PARDS criteria may be applied to pediatric patients with underlying heart or lung disease who meet the criteria for the timing and origin of edema, with the following caveats:
 - a. Underlying disease is not of perinatal origin
 - b. Patient meets the established criteria for radiographic findings
 - c. Acute worsening of oxygenation meets established criteria and is not otherwise explained by the underlying cardiac defect (if applicable)

Table 11. ARDS Definitions

	PARDS ^a	Berlin Definition of ARDS
Timing	Within 7 days of clinical insult	Within 1 wk of clinical insult or new/worsening respiratory symptoms
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid status	Respiratory failure not fully explained by cardiac failure or fluid status: • Requires objective assessment to exclude if no risk factor (underlying clinical condition associated with ARDS) present
Chest imaging	New infiltrate consistent with acute pulmonary parenchymal disease	Bilateral opacities – Not fully explained by effusion, collapse, or nodules
Oxygenation	<i>Noninvasive mechanical ventilation:</i> • Full-face BiPAP or CPAP ≥ 5 cm H₂O • PF ratio ≤ 300 mm Hg OR SF ratio ≤ 264 <i>Invasive mechanical ventilation:</i> • Mild ◦ OI 4 to < 8 OR OSI 5 to < 7.5 • Moderate ◦ OI 8 to < 16 OR OSI 7.5 to < 12.3 • Severe ◦ OI ≥ 16 OR OSI ≥ 12.3	• Mild ◦ PEEP or CPAP ≥ 5 cm H₂O AND ◦ PF ratio > 200–300 mm Hg • Moderate ◦ PEEP ≥ 5 cm H₂O AND ◦ PF ratio > 100–200 mm Hg • Severe ◦ PEEP ≥ 5 cm H₂O AND ◦ PF ratio ≤ 100 mm Hg

^aExcludes patients with lung disease unique to the perinatal period.

ARDS = acute respiratory distress syndrome; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; OI = oxygenation index; OSI = O_2 saturation index; PARDS = pediatric ARDS; PEEP = positive end-expiratory pressure.

- F. Many underlying clinical conditions can result in ARDS. Although the pathologic process is similar, the development and outcomes of ARDS may differ, depending on the underlying clinical condition.
 1. Respiratory infections, including pneumonia – Most common in pediatric patients
 2. Additional causes are numerous, but may include: aspiration, drug ingestion, injury (e.g., contusion, burn, inhalation, submersion), or non-cardiogenic shock

G. Pharmacologic Management in ARDS

1. Pulmonary-specific treatments

- a. Inhaled nitric oxide
 - i. Pulmonary vasodilator with short duration of effect and local action. Vasodilation is mainly isolated to areas with adequate ventilation.
 - ii. Use of inhaled nitric oxide improves oxygenation but has not been shown to improve clinical outcomes.
 - iii. Inhaled nitric oxide can be considered:
 - (a) For patients with documented pulmonary hypertension or severe right ventricular dysfunction
 - (b) For patients with severe hypoxemia as a rescue therapy or bridge to extracorporeal life support
 - iv. If initiated, inhaled nitric oxide should be discontinued in patients without improvement.
- b. Exogenous surfactant
 - i. Many exogenous surfactant studies have evaluated patients with acute hypoxemic respiratory failure outside the neonatal period – evaluated surfactants include calfactant, poractant, beractant, and lucinactant.
 - ii. Evaluation has fairly consistently shown improved oxygenation, though often not sustained improvement.
 - iii. Exogenous surfactant use is not currently recommended.
- c. Corticosteroids
 - i. Because of the overwhelming inflammatory process associated with ARDS, the use of corticosteroids together with other anti-inflammatory therapies is intriguing.
 - ii. Current pediatric data are limited to case series and observational studies, and adult data are also conflicting regarding the benefits of corticosteroids in ARDS.
 - iii. Corticosteroid use is not currently recommended.
- d. The following pulmonary therapies have insufficient data to support their use and are not recommended.
 - i. Heliox
 - ii. Inhaled or intravenous prostanoids: These agents can be used in a fashion similar to inhaled nitric oxide for patients with known pulmonary hypertension or severe right ventricular failure.
 - iii. Anticoagulants (including tissue plasminogen activator and fibrinolytics)
 - iv. Bronchodilators (β -agonist and ipratropium)
 - v. Intravenous acetylcysteine
 - vi. Mucolytics (inhaled acetylcysteine and dornase alfa) – Dornase alfa can be recommended in the cystic fibrosis population, as appropriate.

2. Nonpulmonary treatments

- a. Sedation – See the PICU I chapter for an in-depth discussion of sedative agents.
 - i. Patients should receive minimal effective, goal-directed sedation and reassessed daily.
- b. Neuromuscular blockade (NMB) – See the PICU I chapter for an in-depth discussion of neuromuscular blocking agents.
 - i. NMB may be considered when optimized sedation alone is inadequate to allow for effective mechanical ventilation.
 - ii. The minimum required NMB to facilitate mechanical ventilation and optimize oxygenation should be used.
 - iii. Depth of NMB should be monitored and titrated to the goal depth identified by the interprofessional team and daily holidays are recommended.

- c. Fluid management
 - i. Total fluid goal should be sufficient to maintain intravascular volume and end-organ perfusion and to facilitate O_2 delivery.
 - ii. Goal-directed fluid management should occur by monitoring fluid balance, optimizing intravascular volume but preventing positive fluid balance.

Patient Case

3. D.P. is an 8-month-old male infant (weight 6 kg) with a medical history of chronic lung disease of prematurity, for which he is receiving furosemide at home. He is now in the PICU with a diagnosis of ARDS. He is mechanically ventilated with FiO_2 100%, PEEP 7 cm H_2O , and respiratory rate 24 breaths/minute. His oxygenation continues to worsen, despite advancing his mechanical ventilation. An ECHO reveals suprasystemic right ventricular pressures consistent with pulmonary hypertension. Which pulmonary-specific treatment would best be considered to potentially improve his oxygenation?
- A. Surfactant.
 - B. Nitric oxide.
 - C. Albumin.
 - D. Methylprednisolone.

V. HOSPITAL-ACQUIRED PNEUMONIA AND VENTILATOR-ASSOCIATED PNEUMONIA

- A. Hospital-acquired infections result in worse patient outcomes and increased health care costs.
- B. Hospital-acquired pneumonia (HAP) is a pneumonia not present on admission that develops 48 hours or more after admission to the hospital and is not associated with mechanical ventilation.
- C. VAP develops 48 hours or more after endotracheal intubation that was not present when mechanical ventilation was initiated.
 - 1. VAP is one of the leading hospital-acquired infections in the PICU, occurring at a rate of 2.1–11.6 cases/1000 ventilator-days.
 - 2. VAP has been associated with increased length of PICU stay, increased duration of mechanical ventilation, and increased direct cost.
- D. Because of the effects on patient outcome, focus is placed on preventing HAP and VAP. Prevention strategies may include:
 - 1. Risk factor avoidance
 - a. Of note, not all “modifiable” risk factors can or should be avoided in PICU patients.
 - b. For example:
 - i. Acid-suppressive therapy is recommended in those with a risk of SRMD but should be avoided if patients have no risk factors for SRMD.
 - ii. The overall risks associated with parenteral nutrition outweigh the VAP risk of enteral nutrition.
 - iii. Reduction in immunosuppressive medication therapy may or may not be appropriate.

Table 12. Risk Factors^a for HAP/VAP

Potentially Modifiable Risk Factors	Nonmodifiable Risk Factors
Acid-suppressive therapy Bloodstream infection ^b Bronchoscopy ^b Continuous enteral nutrition Mechanical ventilation and duration > 2 days Need for reintubation or self-extubation ^b NMB Prior antibiotic therapy ^b Steroid administration ^b Supine positioning Transfusion Transport out of PICU Trauma Uncuffed endotracheal tube	Age (older) Genetic syndromes ^b Immunosuppressing condition Lung disease Sex (male) Tracheostomy

^aAs identified in both adult and pediatric studies.

^bIdentified as a risk factor in a meta-analysis of pediatric VAP studies.

HAP = hospital-acquired pneumonia; NMB = neuromuscular blockade; VAP = ventilator-associated pneumonia.

2. Several organizations provide guidance on prevention strategies. In addition to minimizing risk factors, when possible, other prevention strategies include:
 - a. Optimization of infection control, including hand hygiene
 - b. Management of endotracheal tube and ventilator circuit:
 - i. Endotracheal suctioning only when indicated by clinical examination (vs. on a scheduled basis)
 - ii. In-line endotracheal suctioning – Without saline administration
 - iii. Regularly draining the condensation from the ventilator circuit before patient repositioning to prevent condensation from draining into the endotracheal tube
 - iv. Changing the ventilator circuit when visibly soiled or every 7 days
 - c. Glucose control
 - d. Implementing a prevention bundle is recommended – Institute for Healthcare Improvement offers ventilator bundle recommendations, including:
 - i. Head-of-bed elevation to 30–45 degrees
 - ii. Daily sedation holidays and assessment of extubation readiness
 - iii. SRMD prophylaxis, when appropriate
 - iv. Venous thromboembolism prophylaxis (when appropriate in pediatric patients)
 - e. Effectiveness of oral hygiene using chlorhexidine is inconclusive.

E. Specific diagnostic criteria for HAP and VAP in infants and children is found in Figure 3.

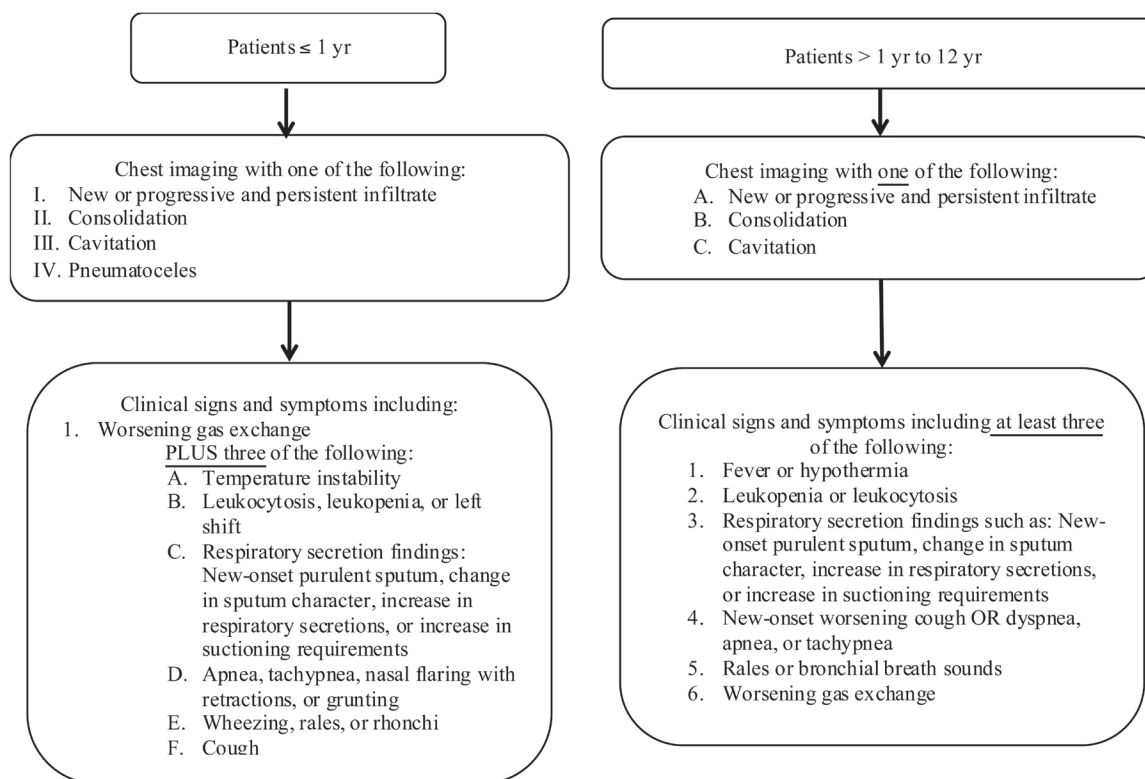


Figure 3. Hospital-acquired/ventilator-associated pneumonia criteria for infants and children.

1. Controversy surrounds the adequacy of these definitions as evaluation criteria for ventilator-associated events in PICU patients.
 - a. Definitions are complex, and inclusion of subjective clinical signs and symptoms may result in variability in reported rates of VAP.
 - b. May not address all clinically important events or infections associated with mechanical ventilation

F. Causative Organisms and Management of HAP/VAP

1. Guidelines for managing HAP/VAP in pediatric patients are unavailable; adult guidelines are often extrapolated to pediatric patients and integrated with known pediatric data.
2. Causative organisms and subsequent empiric therapy are delineated according to:
 - a. Risk factors for specific pathogens and resistant organisms
 - i. Risk factors for multidrug-resistant (MDR) gram-negative organisms that have been identified in studies evaluating bacteremia in pediatric patients include:
 - (a) History of infection or colonization with MDR gram-negative pathogen
 - (b) Exposure to broad-spectrum antibiotic therapy in the past 20 days
 - (c) Prolonged hospitalization
 - (d) High prevalence of MDR gram-negative organisms in the community
 - ii. Additional risk factors are delineated in the HAP/VAP guidelines (see Table 13).
 - iii. Consider dual gram-negative therapy in pediatric patients with HAP/VAP and identified risk factors.

- b. Local antibiogram
 - i. For HAP: Include methicillin-resistant *Staphylococcus aureus* (MRSA) coverage for patients without risk factors if more than 20% of *S. aureus* isolates from the unit of hospitalization are methicillin resistant or if prevalence is unknown.
 - ii. For VAP:
 - (a) Include MRSA coverage for patients without risk factors if more than 10% of *S. aureus* isolates from the unit of hospitalization are methicillin resistant or if prevalence is unknown.
 - (b) Include dual antipseudomonal therapy if:
 - (1) Local susceptibility patterns are unknown
 - (2) More than 10% of local isolates are resistant to an agent being considered for monotherapy
3. Immunocompromised patients may be at risk of additional pathogens, including fungi and viruses.
4. Viruses can be a common cause of lower respiratory tract infections in pediatric patients and can be transmitted while patients are hospitalized.
5. Global impact on local resistance patterns should be considered when choosing empiric therapy.
6. Therapy should be directed to the specific pathogen once culture data are available and discontinued when culture data are negative and suspicion for HAP/VAP is low.
7. For MDR VAP susceptible to aminoglycosides or polymyxins alone, treatment with both inhaled and systemic antibiotics is recommended.

Table 13. Causative Organisms and Empiric Antimicrobial Therapy

Risk Category	Organisms to Cover	Empiric Antimicrobial Therapy
All patients	<i>Staphylococcus aureus</i> (MSSA) <i>Pseudomonas aeruginosa</i> Other gram-negative bacilli	Antipseudomonal penicillin: Piperacillin/tazobactam OR Cephalosporin: Cefepime Ceftazidime OR Carbapenem: Meropenem Imipenem/cilastatin OR Aztreonam
Any of the following at the onset of VAP: Septic shock ARDS ≥ 5 days of hospitalization Acute RRT	As above for all patients <i>PLUS</i> MDR organisms	Use of two antipseudomonal agents, including an antipseudomonal β -lactam PLUS an agent from a different class: Antipseudomonal fluoroquinolone: ciprofloxacin or levofloxacin OR
HAP with high risk of mortality: Need for ventilator support for pneumonia Septic shock	As above for all patients <i>PLUS</i> MDR organisms	Aminoglycoside – Extended-interval dosing recommended in HAP/VAP guideline OR Polymyxin

Table 13. Causative Organisms and Empiric Antimicrobial Therapy (*continued*)

Risk Category	Organisms to Cover	Empiric Antimicrobial Therapy
Prior IV antibiotic coverage in the past 90 days	As above for all patients <i>PLUS</i> MRSA MDR organisms MDR <i>P. aeruginosa</i>	MRSA coverage with: Vancomycin OR linezolid Use of two antipseudomonal agents, including an antipseudomonal β -lactam PLUS an agent from a different class such as: Antipseudomonal fluoroquinolone: Ciprofloxacin or levofloxacin OR Aminoglycoside – Extended-interval dosing recommended in HAP/VAP guideline OR Polymyxin

MDR = multidrug resistant; MRSA = methicillin-resistant *Staphylococcus aureus*; RRT = renal replacement therapy.

8. Therapy duration

- a. Current guidelines recommend 7 days for all patients.
- b. Duration of 8 days versus 15 days – Multicenter, randomized controlled trial of adult patients compared a treatment duration of 8 days with 15 days for VAP therapy.
 - i. No difference in mortality with shorter duration compared with longer duration
 - ii. Higher rate of microbiological recurrence of non-lactose-fermenting gram-negative rods (*Pseudomonas aeruginosa* and *Acinetobacter* spp.) with 8 days of therapy
 - iii. In those with recurrent infections, risk of MDR organisms was lower in the 8-day group.

Patient Case

4. T.D. is a 6-year-old girl (weight 22 kg) with a medical history pertinent for developmental delay, constipation, and chronic lung disease of prematurity. Admitted to the PICU 3 days ago after a traumatic brain injury, she underwent emergency neurosurgical intervention, and an intraventricular drain remains in place. A double-lumen temporary central line was placed during the surgical procedure and remains in place. She has been intubated and receiving mechanical ventilation since the day of admission. Today, her maximum temperature is 102.5°F, respiratory rate is 42 breaths/minute, and heart rate is 120 beats/minute. A tracheal aspirate obtained by a protected brush specimen this morning shows many gram-negative rods and many WBCs on stain. Which is the best empirical therapy for T.D.?
 - A. Levofloxacin 10 mg/kg/dose intravenously twice daily and clindamycin 15 mg/kg intravenously every 8 hours.
 - B. Ampicillin/sulbactam 50 mg/kg/dose (of ampicillin component) intravenously every 6 hours and vancomycin 15 mg/kg/dose intravenously every 6 hours.
 - C. Gentamicin 7.5 mg/kg/dose intravenously every 24 hours and vancomycin 15 mg/kg/dose intravenously every 6 hours.
 - D. Cefepime 50 mg/kg/dose intravenously every 8 hours and vancomycin 15 mg/kg/dose intravenously every 6 hours.

VI. STRESS-RELATED MUCOSAL DISEASE AND UPPER GASTROINTESTINAL BLEEDING

- A. SRMD is an acquired disease of the GI mucosa that can occur during critical illness.
 - 1. May result in UGIB with a high risk of morbidity and mortality
 - a. Signs of UGIB may include hematemesis, hematochezia, and frank or coffee-ground secretions from gastric tubes.
 - b. Of greatest concern is clinically significant bleeding, defined as UGIB with:
 - i. Hemodynamic instability
 - ii. A clinically relevant decrease in Hgb
 - iii. Need for red blood cell transfusion
 - iv. Need for surgery
 - c. Clinically significant UGIB affects patients' length of stay in the PICU and need for blood transfusions compared with patients with nonsignificant UGIB and causes longer durations of mechanical ventilation than in those without UGIB.
 - d. Cost of care is increased for PICU patients with clinically significant UGIB compared with nonsignificant UGIB and those without UGIB.
 - e. Progress in the support of the critically ill patient, including hemodynamic optimization, improved oxygenation, and sepsis management, may contribute to the decreased rates in clinical significant UGIB shown in more recent adult studies.
 - 2. The incidence of UGIB in PICU varies by definition used and population.
 - a. Any UGIB: 6.4%–51.8%
 - b. Clinically significant UGIB: 0.4%–3.6%
 - 3. These risks have prompted the pursuit of prevention strategies, including pharmacologic prophylaxis.
- B. Pathophysiology of SRMD
 - 1. Multifactorial process resulting in the breakdown of the GI mucosa with resultant injury and ulceration
 - 2. Factors resulting in mucosal damage include:
 - a. Splanchnic hypoperfusion resulting in mucosal ischemia
 - b. Gastric acid secretion in the face of impaired gastric motility
 - c. Reperfusion injury resulting in mucosal cell death
- C. Risk Factors for SRMD Bleeding
 - 1. Several risk factors have been identified in adult and pediatric patients.
 - 2. Often, adult defined risk factors are also applied to the pediatric population.
 - 3. Some factors may be independent predictors of risk, whereas others contribute to a cumulative risk.
 - 4. Risk increases with increasing number of risk factors.

Table 14. Risk Factors Associated with SRMD in Critical Illness

Independent Risk Factors		Factors Contributing to Cumulative Risk
Pediatric	Adult	
Coagulopathy ^a PRISM score ≥ 10 Respiratory failure ^b In mechanically ventilated: High pressure ventilation (positive inspiratory pressure ≥ 25 cm H ₂ O) Organ failure	Coagulopathy Respiratory failure Shock Multiple trauma	Acute hepatic failure Acute renal failure Anticoagulation Burn injury (> 35% total body surface area) High-dose corticosteroids (> 250 mg/day of hydrocortisone) History of GI bleed Hypotension Low intrinsic gastric pH Major surgery (> 4 hr) Sepsis Severe head or spinal cord injury

^aSeveral definitions of coagulopathy have been used in studies, including prolonged partial thromboplastin time, prolonged prothrombin time, INR > 1.5, and platelet count < 100,000/mm³.

^bNeed for mechanical ventilation.

PRISM = Pediatric Risk of Mortality Score.

D. SRMD Bleeding Prevention Strategies

1. Prevention strategies have not extensively been studied in the pediatric population, especially with respect to optimal drug therapy and the number of risk factors requiring pharmacotherapy.
2. Consider pharmacotherapy for one independent risk factor or at least cumulative risk factors.
3. Medication options – See the Gastroenterology/Hepatology chapter for more medication details.
 - a. Histamine-2 receptor antagonist (H₂RA)
 - i. Famotidine is currently preferred.
 - (a) Available dosing for all age groups of pediatric patients
 - (b) Available both enterally and intravenously
 - ii. Cimetidine is generally avoided because of adverse effects and drug interactions.
 - iii. Ranitidine is currently unavailable on the U.S. market due to concerns for manufacturing impurities.
 - iv. Tolerance to H₂RA effects can develop.
 - b. PPIs
 - i. Esomeprazole, lansoprazole, omeprazole, rabeprazole, and pantoprazole have available dosing recommendations for all pediatric patient age groups.
 - (a) Dexlansoprazole is approved in children and adolescents older than 11 years.
 - ii. Esomeprazole and pantoprazole are available as intravenous formulations.
 - iii. Tolerance to effect does not develop.
 - iv. Hypersecretion of gastric acid may occur with discontinuation.
 - c. Sucralfate
 - i. Generally not considered first line
 - ii. May clog enteral gastric feeding tubes
 - iii. May interfere with the absorption of other enterally administered medications, requiring separation of dosing

-
- iv. Adverse effects of concern in PICU patients:
 - (a) Constipation
 - (b) Aluminum accumulation in renal dysfunction
 - d. Medication therapy should be discontinued once risk factors are resolved.
 - 4. Controversies in SRMB:
 - a. H₂RA versus PPI:
 - i. No definitive data suggest that PPIs are more effective than H₂RAs at preventing UGIB.
 - ii. Compared with placebo, neither class was more likely to decrease clinically significant UGIB.
 - b. Intravenous versus enteral therapy
 - i. Data do not support that the intravenous route improves efficacy; enteral therapy should be utilized where possible.
 - ii. Each class contains at least one agent that can be administered by postpyloric feeding tubes.
 - c. Pneumonia risk – One pediatric study compared the risk of pneumonia in PICU patients receiving sucralfate, ranitidine, or omeprazole and found no increased risk of pneumonia compared with patients not receiving SRMD therapy.
 - d. Multiple retrospective studies have identified an association between PPI use and increased *Clostridioides difficile* rates in both children and adults, but many confounding factors limit interpretability.
 - 5. Enteral feeding
 - a. Data are inconsistent on the ability of enteral feeding to prevent UGIB.
 - b. Not universally recommended to prevent SRMD
 - E. Pharmacotherapy Management of Clinically Significant UGIB
 - 1. Goals of therapy are to control bleeding, generally in conjunction with endoscopic intervention, and to prevent rebleeding.
 - 2. Hemodynamic stabilization: Administer isotonic crystalloids and blood products as indicated.
 - 3. Acid suppression
 - a. PPIs are preferred.
 - i. Platelet function is inhibited in acidic pH. A pH of 6 or greater is ideal for platelet aggregation, which may not consistently be achieved by H₂RA therapy.
 - ii. Efficacy of continuous infusions versus high-dose bolus intravenous therapy for preventing rebleeding is controversial.
 - (a) Continuous infusion dosing of esomeprazole or pantoprazole can be used, though dosing is not well established in pediatric patients.
 - (b) Administer the bolus dose, followed by the continuous infusion:
 - (1) Non–weight-based dosing: 80 mg intravenously once, followed by 8 mg/hour
 - (2) Weight-based dosing: 1 mg/kg intravenously once, followed by 0.1 mg/kg/hour
 - b. Intravenous therapy should be continued for the first 72 hours.
 - c. May decrease the need for endoscopic therapy and the risk of rebleeding
 - 4. Vasoactive medication
 - a. May minimize variceal bleeding
 - b. Octreotide is preferred to vasopressin for both efficacy and safety reasons.
-

Patient Case

5. G.I. is a 7-year-old boy (weight 25 kg) who presents to the PICU intubated and mechanically ventilated for respiratory failure secondary to status asthmaticus. His pertinent medical history includes asthma and gastroesophageal reflux disease. Before intubation, he received albuterol/ipratropium x 3 doses, methylprednisolone 50 mg intravenously once, and magnesium sulfate 2 g intravenously once. On the patient's presentation to the PICU, the nurse reports red-tinged secretions after suctioning and coffee-ground nasogastric output. His laboratory values include K 3.1 mEq/L, SCr 1.6 mg/dL, Hgb 10.5 g/dL, and Hct 35%. Which is the best initial pharmacotherapy option for this patient?
- A. Octreotide 25 mcg intravenously x 1.
 - B. Famotidine 12.5 mg intravenously every 12 hours.
 - C. Pantoprazole 20 mg intravenously once daily.
 - D. Sucralfate 1 g by nasogastric tube every 8 hours.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

The patient has DKA, given his decreased venous pH and HCO_3^- values as well as his moderate ketones (Answers A and C are incorrect). For management of DKA, resuscitation fluids should be administered at a dose of 10 mL/kg infused over 30–60 minutes according to current practice guidelines. (Answer B is correct); a repeat bolus may be administered if tissue perfusion remains inadequate. Although resuscitation fluids can be given over shorter durations in patients with HHS or DKA presenting in shock, this patient's peripheral pulses are good, and his altered mental status could indicate clinically overt cerebral edema; therefore, rapid fluid administration should be avoided without clear shock (Answers C and D are incorrect). With DKA, insulin would be initiated as a continuous infusion after resuscitation fluids (Answer B is correct). Insulin boluses are never recommended in pediatric patients (Answers C and D are incorrect). With HHS, continuous insulin would be initiated once the rate of glucose decrease was less than 50 mg/dL/hour with fluids alone (Answer A is incorrect).

2. Answer: A

The patient's previous seizures have responded to benzodiazepines; therefore, lorazepam would be the best emergent initial agent for her (Answer A is correct). While gaining control of the patient's seizure, a plan should be made to correct her lower sodium concentration, though sodium is unlikely to have caused her seizure; thus, 0.9% sodium chloride would not be the initial choice (Answer B is incorrect). Phenobarbital could be used as urgent control therapy, but benzodiazepines would be initiated first, and 20 mg would not be the appropriate dose for this patient weighing 52 kg (Answer C is incorrect). Propofol is reserved for RSE; this patient would not be considered to have RSE because her seizures have responded to first-line therapy, and urgent control therapy has not been tried (Answer D is incorrect).

3. Answer: B

Many ARDS therapies have limited supportive evidence, and large controlled randomized trials either have not been conducted or have shown no meaningful difference. Because this patient's ECHO findings are consistent with pulmonary hypertension and poor

oxygenation, a course of inhaled nitric oxide would be reasonable (Answer B is correct). Surfactant has been shown to improve oxygenation in some studies; however, it has not improved clinical outcomes and is not currently recommended in ARDS (Answer A is incorrect). No pediatric trials have evaluated corticosteroids, and the data from adult studies are contradictory; therefore, corticosteroids are not recommended in pediatric patients with ARDS (Answer D is incorrect). Data are insufficient to recommend the use of bronchodilators (Answer C is incorrect).

4. Answer: D

Because this patient was admitted after a trauma and has been intubated and receiving mechanical ventilation for more than 2 days, she is at increased risk of VAP. The most likely organisms for which this patient should empirically be covered include gram-negative bacilli and *S. aureus*. Despite having Gram stain information from the tracheal aspirate, broad empiric coverage should be initiated pending culture results. Of the available options, cefepime, which will provide coverage for susceptible gram-negative bacilli and susceptible *Staphylococcus*, together with vancomycin for coverage of resistant gram-positive organisms, would be best, pending culture results (Answer D is correct). Levofloxacin covers susceptible gram-negative bacilli and susceptible *Staphylococcus*, though it is generally recommended in combination with an antipseudomonal β -lactam for patients at risk of developing HAP/VAP from MDR organisms. In addition, clindamycin is inappropriate empiric coverage for health care-acquired MRSA infections (Answer A is incorrect). Neither ampicillin/sulbactam nor gentamicin monotherapy is appropriate coverage for *P. aeruginosa* (Answers B and C are incorrect).

5. Answer: C

This patient likely has clinically nonsignificant UGIB, potentially from SRMD. He does not have a clinically overt UGIB, as shown by his normal Hgb/Hct, and has no history consistent with concern for variceal bleeding, for which octreotide might be indicated (Answer A is incorrect). He does not have an acute GI bleed because his Hgb and Hct are moderately reduced. He should be treated for the prevention of clinically overt UGIB, for which the best option would be either an H_2 RA or a PPI.

The patient's SCr indicates the presence of acute kidney injury; therefore, famotidine dosing would need to be adjusted for decreased renal function (Answer B is incorrect). Of the options, pantoprazole would be best, and if the patient has an ulcer that is the source of his bleeding, pantoprazole would provide sufficient acid suppression, which should allow for platelet aggregation and healing (Answer C is correct). Sucralfate is not a first-line choice and could clog the patient's enteral feeding tubes (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

This patient has respiratory alkalosis. His pH is elevated at 7.48 (normal 7.35–7.45). The pH value alone indicates alkalosis (Answer D is correct), not acidosis (Answers A and B are incorrect). Analyzing the P_{CO_2} and HCO_3^- next will determine whether the alkalosis is respiratory or metabolic. The P_{CO_2} is 30 mm Hg, which is low (normal 35–45 mm Hg) (Answer D is correct), and the HCO_3^- is 22 mEq/L, which is normal but on the low end of normal (Answer C is incorrect). Therefore, this patient's primary acid-base disorder is respiratory, which is consistent with the patient's diagnosis of pneumonia.

2. Answer: A

This patient has metabolic acidosis with an anion gap. Her pH is 7.3, which is low and indicates an acidosis (Answer A is correct; Answers C and D are incorrect). Her low HCO_3^- of 18 mEq/L (normal 22–28 mEq/L) indicates a metabolic process (Answer A is correct). Her P_{CO_2} is 30 mm Hg, which is low, likely indicating some compensation for the present acidosis (Answer B is incorrect).

3. Answer: D

This patient was admitted because she had SE. She was seizing for about 15 minutes, which can result in muscle breakdown and lactate production (Answer D is correct). Elevated lactate concentrations result in an elevated anion gap metabolic acidosis. Hypoxemia secondary to seizures can result in acid-base disturbances, but the primary disturbance would be respiratory alkalosis (Answer A is incorrect). Although DKA can result in an elevated anion gap metabolic acidosis, hyperglycemia without ketosis is not a cause of metabolic acidosis; also, prolonged seizures generally lead to hypoglycemia (Answer B is incorrect). This patient's SCr is 0.3 mg/dL, which is not consistent with renal dysfunction (Answer C is incorrect).

4. Answer: C

Once metabolic acidosis has been determined, the next step is to calculate an anion gap to determine whether the acidosis is caused by unmeasured anions or HCO_3^- losses. To calculate the anion gap, the following equation is used: $Na^+ - (Cl^- + HCO_3^-)$. For the laboratory values presented, $137 - (100 + 18) = 19$ (Answer C is correct; Answers A, B, and D are incorrect).

5. Answer: B

This patient has new-onset diabetes mellitus presenting with DKA. Adequate resuscitation is the initial treatment phase for all patients with DKA and should occur while awaiting laboratory values. Even if the laboratory values are not yet available, the patient can be rehydrated. Current guidelines suggest that resuscitation with 10 mL/kg (for this patient, 200 mL) intravenously over 30–60 minutes is appropriate for patients presenting without shock. This patient has received only 5 mL/kg; therefore, administering the remainder of the fluid resuscitation, 100 mL over 30–60 minutes, would be best (Answer B is correct). After administration of 10 mL/kg, an additional fluid bolus may be considered if tissue perfusion remains inadequate. Arterial blood gas tests are not needed, though a venous blood gas test to classify severity should be obtained (Answer A is incorrect). Although in specific circumstances, potassium replacement may occur in the resuscitation phase, this patient has no indications of life-threatening hypokalemia; thus, potassium replacement can be initiated once the laboratory values are available (Answer C is incorrect). Insulin should not be initiated until after fluid resuscitation, and early initiation may be associated with an increased risk of clinically overt cerebral edema (Answer D is incorrect).

6. Answer: A

Initial glucose correction with fluid therapy in HHS is generally 75–100 mg/dL/hour (Answer A is correct). A decrease of less than 50 mg/dL/hour would require the addition of insulin therapy, which would be used to maintain a decrease of 50–75 mg/dL/hour once initiated (Answers B and D are incorrect). A decrease of greater than 100 mg/dL/hour would be too rapid and would require the addition of dextrose 2.5%–5% to the replacement fluids (Answer C is incorrect).

7. Answer: B

The best emergent initial option for this patient would be lorazepam 4 mg intravenously because the patient has intravenous access, and his initial response to benzodiazepines makes repeat dosing an appropriate plan (Answer B is correct). Although another dose of rectal diazepam could be given, 5 mg is not the correct dose for this patient; also, rectal diazepam has a slower onset than intravenous lorazepam, and alternative routes need only be used when intravenous access is not available.

(Answer A is incorrect). Either phenobarbital or continuous infusion midazolam may be considered if the patient does not respond to an intermittent intravenous dose of lorazepam (Answers C and D are incorrect).

8. Answer: C

Fosphenytoin 20 mg PE/kg (160 mg) or phenytoin 20 mg/kg (160 mg) would be the next best choice. The fosphenytoin dose can be administered at a rate of 3 mg/kg/minute (24 mg/minute) over 5–6 minutes (Answer C is correct). The phenytoin dose can be administered at 1 mg/kg/minute (8 mg/minute) over 15–20 minutes (Answer B is incorrect). Administering a third dose of benzodiazepine without seizure cessation after the first two doses is not recommended (Answer A is incorrect). Valproic acid can be used as an urgent control agent in SE; however, valproic acid would generally only be considered over fosphenytoin or phenytoin in patients with generalized epilepsy, and this patient has no history of seizure. In addition, the risk of hepatotoxicity is increased in patients younger than 2 years (Answer D is incorrect).

9. Answer: C

There is little or no definitive evidence for medication therapy in pediatric patients. Adding NMB can be considered when adequate oxygenation is not achieved by sedation optimization (Answer C is correct). Providing optimal sedation to facilitate mechanical ventilation is recommended, for which fentanyl and midazolam would be reasonable; however, adding another as-needed medication in a clinically worsening patient would probably not enhance sedation or improve oxygenation (Answer B is incorrect). Studies using corticosteroids for ARDS in adults have had inconsistent results on its effect on outcomes, and pediatric data are currently narrow in clinical applicability because of methodologic limitations; thus, corticosteroids cannot be recommended (Answer A is incorrect). Inhaled nitric oxide is indicated in patients with known pulmonary hypertension or right ventricular failure, which this patient does not currently have (Answer D is incorrect).

10. Answer: A

In addition to the oral hygiene and head of the bed elevation, the patient should have daily sedation holidays to assess for extubation readiness, as recommended in the Institute for Healthcare Improvement VAP bundle (Answer A is correct). Because of the risk of SRMD, stress ulcer prophylaxis is appropriate and should be continued; however, there is no indication to switch this

patient or add a PPI for SRMD prophylaxis (Answers B and D are incorrect). Venous thromboembolism prophylaxis is indicated in the VAP bundle and should be used when appropriate; however, this patient is likely low risk given her age and lack of central venous access, so this would be unnecessary (Answer C is incorrect).

11. Answer: C

This patient, who has signs and symptoms consistent with VAP, has been intubated for more than 2 weeks; therefore, empiric treatment should provide coverage for organisms common in VAP and for those with risk factors for resistant organisms, including *Pseudomonas* and MRSA (Answer C is correct). Ampicillin/sulbactam, ampicillin plus gentamicin, and ceftriaxone fail to provide adequate coverage of *Pseudomonas* and are not appropriate empiric coverage for VAP in the PICU (Answers A, B, and D are incorrect).

12. Answer: B

This patient is at risk of SRMD secondary to an elevated INR, mechanical ventilation, shock, and acute renal failure (estimated creatinine clearance 36–39 mL/minute/1.73 m²). Thus, pharmacologic prophylaxis should be administered (Answer D is incorrect). Either an H₂RA or a PPI provided enterally or intravenously would be an appropriate first-line choice. If famotidine is chosen, it should be renally dose adjusted because of the patient's acute kidney injury; thus, it should not be dosed at 1 mg/kg/dose intravenously every 12 hours (Answer A is incorrect). A PPI such as lansoprazole would be an appropriate first-line choice and would not require renal dose adjustment (Answer B is correct). Sucralfate is not recommended as a first-line choice, and aluminum accumulation can occur in patients with renal insufficiency (Answer C is incorrect).

13. Answer: B

This patient has several risk factors for possible UGIB from SRMD. Respiratory failure has been identified as an independent risk factor in both adult and pediatric patients (Answer B is correct). A history of a GI bleed and septic shock are both factors that contribute cumulative risk, making them risk factors in this patient, but they have not been identified as independent predictors of risk in pediatric patients (Answers C and D are incorrect). In addition, the patient's septic shock has resolved; therefore, this would no longer be considered a risk (Answer D is incorrect). Prematurity is not a known risk predictor (Answer A is incorrect).

NEONATOLOGY

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NEONATOLOGY

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Learning Objectives

1. Compare the exogenous surfactant products available for the prevention and treatment of respiratory distress syndrome.
2. Describe the pharmacologic options for the prevention and treatment of bronchopulmonary dysplasia.
3. Describe the use of methylxanthines for the treatment of apnea of prematurity.
4. Describe the role of indomethacin for the prevention of intraventricular hemorrhage.
5. Compare the drugs available and the various therapeutic approaches (i.e., prophylaxis, early treatment, delayed treatment) for patent ductus arteriosus.
6. Discuss the supportive and targeted therapies for persistent pulmonary hypertension of the newborn.
7. Discuss therapeutic strategies to prevent and treat necrotizing enterocolitis.
8. Identify potential treatment options for common congenitally acquired infections, including herpes, syphilis, toxoplasmosis, cytomegalovirus, and hepatitis B.
9. Discuss the assessment and management of neonatal abstinence syndrome.
10. Explain important considerations, including the risk of fetal/neonatal harm and factors affecting drug transfer across the placenta or into breast milk, when choosing drugs for use during pregnancy or lactation.

Abbreviations in This Chapter

ALT	Alanine aminotransferase
BPD	Bronchopulmonary dysplasia
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal fluid
ECHO	Echocardiogram
FiO ₂	Fraction of inspired oxygen
HBIG	Hepatitis B immune globulin
HBsAg	Hepatitis B surface antigen
HSV	Herpes simplex virus
IVH	Intraventricular hemorrhage
NAS	Neonatal abstinence syndrome
NEC	Necrotizing enterocolitis

NICU	Neonatal intensive care unit
OI	Oxygenation index
PCR	Polymerase chain reaction
PDA	Patent ductus arteriosus
PDE	Phosphodiesterase
PPHN	Persistent pulmonary hypertension of the newborn
RDS	Respiratory distress syndrome
RPR	Rapid plasma reagin (test)
VDRL	Venereal Disease Research Laboratory (test for syphilis)

Self-Assessment Questions

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

1. As a member of your institution's pharmacy and therapeutics committee, you are asked to evaluate the available surfactant products and select one for adding to the institution's formulary. Which statement best justifies your selection?
 - A. The selected product has the highest content of surfactant protein B (SP-B).
 - B. The selected product has the most rapid onset of action.
 - C. The selected product has been shown to reduce the need for mechanical ventilation.
 - D. The selected product has been shown to reduce the risk of bronchopulmonary dysplasia (BPD).
2. When comparing the literature evaluating the efficacy of various treatments for patent ductus arteriosus (PDA), you find a case series of 10 patients treated with acetaminophen at an average age of 10 days and a retrospective study of 160 patients treated with indomethacin at an average age of 11 days. The reported closure rates after the first course of therapy were 100% with acetaminophen and 72% with indomethacin. Which best explains the disparity in closure rates between the two therapies?
 - A. Heterogeneity between the two study populations.
 - B. Inadequate statistical power.
 - C. Publication bias.
 - D. Superior efficacy of acetaminophen.

3. You work in a neonatal intensive care unit (NICU) that is considering implementing a protocol using indomethacin for intraventricular hemorrhage (IVH) prophylaxis. Which outcome is best supported by results of clinical trials and best justifies such a protocol?
- A. Improved long-term neurodevelopmental outcomes.
 - B. Reduced mortality.
 - C. Reduced incidence of PDA.
 - D. Reduced incidence of severe IVH.
4. A 750-g girl born at 26 weeks' gestational age was initiated on caffeine citrate for the prevention of apnea of prematurity. Initially, an intravenous loading dose of 20 mg/kg/dose was given, followed by a maintenance dose of 8 mg/kg/dose every 24 hours. One week later, the neonate is having more episodes of apnea. Other causes of apnea (e.g., sepsis) were ruled out, so the caffeine maintenance dose was increased to 10 mg/kg/dose every 24 hours. Current vital signs and laboratory results include heart rate 190 bpm, blood pressure 50/30 mmHg, respiratory rate 40, and serum creatinine 0.4 mg/dL. The neonate is tolerating full enteral feedings. The physician is concerned about potential toxicity because the dose is at the higher end of the recommended range. Which monitoring value would be most indicative of caffeine toxicity?
- A. Heart rate.
 - B. Renal function.
 - C. Serum concentration.
 - D. Signs of gastroesophageal reflux.
5. A 2500-g boy is born at 35 weeks' gestational age to a mother whose hepatitis B surface antigen (HBsAg) status is unknown. Which is the best recommendation regarding postexposure prophylaxis for this neonate?
- A. Give the hepatitis B vaccine within 12 hours of birth; administer hepatitis B immune globulin (HBIG) within 7 days if the maternal HBsAg is positive.
 - B. Give the hepatitis B vaccine and HBIG within 12 hours of life.
 - C. Give the hepatitis B vaccine birth dose; HBIG is not indicated.
 - D. Wait for the results of the maternal HBsAg test before giving the hepatitis B vaccine or HBIG.
6. A 2100-g girl born at 34 weeks' gestational age develops seizures 2 weeks after birth. Serum electrolytes and glucose are normal. Vesicular lesions are noted on the tongue and buccal mucosa. In addition to anticonvulsant therapy, ampicillin, ceftazidime, and acyclovir are initiated for suspected meningitis. Two days later, the herpes simplex virus (HSV) polymerase chain reaction (PCR) from the cerebrospinal fluid (CSF) is positive and the bacterial cultures are negative, so ampicillin and ceftazidime are discontinued. Serum alanine aminotransferase (ALT) has remained normal. Which is the best recommendation regarding this neonate's antiviral therapy?
- A. Continue intravenous acyclovir 20 mg/kg/dose every 8 hours for 7 days.
 - B. Continue intravenous acyclovir 20 mg/kg/dose every 8 hours for 10 days.
 - C. Continue intravenous acyclovir 20 mg/kg/dose every 8 hours for 14 days.
 - D. Continue intravenous acyclovir 20 mg/kg/dose every 8 hours for 21 days.
7. A 450-g boy who was born at 24 weeks' gestational age received three doses of surfactant for respiratory distress syndrome (RDS). Because of his very low birth weight, presence of a PDA, and severity of RDS, the medical team would like to initiate therapy to prevent progression to BPD. According to clinical trials, which is most likely to prevent BPD in premature neonates with risk factors similar to this neonate's?
- A. Azithromycin.
 - B. Indomethacin.
 - C. Inhaled nitric oxide.
 - D. Vitamin A.

-
8. When benchmarking against similar NICUs, your unit finds a higher than average rate of necrotizing enterocolitis (NEC). The medical team would like to develop a protocol to standardize care of neonates at highest risk of developing NEC. Which intervention is most likely to be beneficial in reducing the incidence of NEC in high-risk neonates?
- A. Initiate trophic feeding at 7 days of age.
 - B. Administer oral probiotics until 34 weeks' postmenstrual age is reached.
 - C. Administer oral antibiotics until full enteral feeding is achieved.
 - D. Administer histamine-2 receptor antagonists until enteral feeds are initiated.
9. A 39 weeks' gestational age boy was born to a mother with a history of sickle cell disease treated with chronic hydrocodone plus acetaminophen. He is admitted to the NICU for monitoring for withdrawal symptoms. In the past 12 hours, his Finnegan scores are 10, 8, 9, and 11 (evaluated every 3 hours) despite non-pharmacologic interventions. Which recommendation would be best for managing this neonate?
- A. Initiate clonidine.
 - B. Initiate morphine.
 - C. Initiate phenobarbital.
 - D. Treatment is not indicated because withdrawal symptoms are not severe enough.
10. A new drug for the treatment of hypertension was shown to be teratogenic in rat models, but there are no reports of its use in pregnant women. Which characteristic is most likely to allow the drug to cross the placental barrier into the fetal circulation?
- A. High molecular weight (greater than 500 Da).
 - B. Hydrophilicity.
 - C. Low protein binding.
 - D. Long half-life.
11. You are working with the neonatologists in your unit to develop a treatment protocol for NEC. Which organism is most important to cover with your recommended empiric antibiotic regimen?
- A. *Candida albicans*.
 - B. *Escherichia coli*.
 - C. Group B *Streptococcus*.
 - D. *Listeria monocytogenes*.
12. A breastfeeding mother presents with newly diagnosed hypertension. The medical team asks you to suggest ways to minimize neonatal risks and exposure from the treatment while still allowing the mother to breastfeed. Which recommendation is most likely to achieve this goal?
- A. Choose a drug with a relatively long half-life.
 - B. Choose a drug that is not highly protein bound.
 - C. Advise the mother to feed when her serum concentrations of the drug are likely to be lowest during the day.
 - D. Select the lowest effective treatment dose.
13. A boy born at 42 weeks' gestational age has pulmonary hypertension secondary to meconium aspiration syndrome. Sedation, vasopressor therapy, and mechanical ventilation are initiated as supportive therapy. Which is the best initial intervention to lower his pulmonary pressures?
- A. Beractant.
 - B. Epoprostenol.
 - C. Inhaled nitric oxide.
 - D. Vecuronium.
-

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.2, 1.3, 1.4, 1.5
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.3, 2.4, 2.5
3. Domain 3: Information Management, Research, and Education; Task(s): 3.2, 3.4

I. RESPIRATORY DISTRESS SYNDROME**A. Background**

1. Common cause of neonatal morbidity and mortality before the development of exogenous surfactant
2. Immaturity of type II alveolar cells results in endogenous surfactant deficiency.
 - a. Surfactant deficiency increases alveolar surface tension and decreases lung compliance.
 - b. Atelectasis causes pulmonary vasoconstriction, impaired gas exchange, and ischemia of lung tissue. The resulting lung epithelial sloughing and edema forms hyaline membranes.
 - c. Surfactant synthesis and storage begins at about 16 weeks' gestation.
 - i. Secretion of surfactant in the fetus begins later, at 30–32 weeks' gestation, and is stimulated by endogenous cortisol.
 - ii. By 34–36 weeks' gestation, adequate amounts of endogenous surfactant are produced to support normal lung function.
3. Components of endogenous surfactant
 - a. Phosphatidylcholine (70%)
 - b. Surfactant proteins (SP) (8%)
 - i. SP-B and SP-C facilitate adsorption and spread of phospholipids at the air/fluid interface within the alveoli, thus preventing collapse during expiration.
 - ii. SP-A stimulates host defense and enhances recycling of surfactant.
 - iii. SP-D is thought to stimulate host defense mechanisms.
 - c. Natural lipids (8%), phospholipids (6%), and phosphatidylglycerol (8%)
 - d. Phosphatidylcholine, SP-B, and SP-C are most crucial for surfactant function.

B. Clinical Presentation

1. Signs and symptoms
 - a. Tachypnea, grunting, nasal flaring, retractions, hypoxia, and cyanosis occurring soon after birth
 - b. Chest radiograph reveals homogeneous opaque infiltrates and air bronchograms; classic “ground-glass” appearance.
2. Risk factors
 - a. Prematurity
 - i. Most common in neonates born before 28 weeks' gestation
 - ii. Rare (less than 5%) in neonates born after 34 weeks' gestation
 - iii. Lack of antenatal steroid administration further increases the risk of RDS in the premature neonate.
 - b. Male sex
 - c. Maternal diabetes
 - d. White race

Patient Case

1. A 660-g boy born by vaginal delivery at 24 weeks' gestational age had a poor respiratory effort, grunting, and retractions at birth and required intubation with 100% oxygen in the delivery room. Apgar scores were 4 at 1 minute, 6 at 5 minutes, and 8 at 10 minutes. Maternal obstetric history was significant for preterm labor, tobacco smoking, and no prenatal care. Because of the lack of prenatal care and a precipitous delivery, no antenatal steroids were administered. An initial blood gas showed pH 7.1, P_{CO_2} 73, P_{O_2} 71, and base deficit 10. A chest radiograph is ordered, and the result is pending. After transfer to the NICU at 15 minutes of life, he continues to require 100% oxygen and high peak inspiratory pressures to maintain adequate oxygen saturations. Which is the best recommendation regarding surfactant therapy for this patient?
 - A. Surfactant therapy should be withheld pending radiographic findings confirming RDS.
 - B. Prophylactic surfactant therapy should be administered because this neonate is at high risk of developing RDS.
 - C. Early surfactant rescue therapy should be administered because this neonate's presentation is consistent with RDS.
 - D. Surfactant rescue therapy should be delayed to avoid overtreatment of this neonate, whose symptoms of RDS may resolve spontaneously.

C. Pharmacologic Management

1. Exogenous surfactant replacement
 - a. Has significantly reduced mortality and respiratory morbidity since use became routine in the early 1990s.
 - b. Comparison of surfactant products: Composition and dosing

Table 1. Comparison of Surfactant Products

Product	Source	Main Phospholipids	Phospholipid Concentration	Proteins (% of total protein)	Dose (mL/kg)	Phospholipid per Dose (mg/kg)	Dosing Interval ^a (hours)
NATURAL PRODUCTS							
Beractant	Bovine	DPPC (45%–65%), PG	25 mg/mL	SP-B (< 5%), SP-C (99%)	4	100	6
Calfactant	Bovine calf	DPPC (45%), PG	35 mg/mL	SP-B (40%), SP-C (60%)	3	105	12
Poractant	Porcine	DPPC (40%), PG	76 mg/mL	SP-B (45%), SP-C (55%)	2.5 (first dose) and 1.25 (subsequent)	200/100	12
SYNTHETIC PRODUCTS							
Colfosceril ^b	Synthetic	DPPC (100%)	13.5 mg/mL	None	5	67.5	12
Lucinactant ^b	Synthetic	DPPC (75%), POPG	30 mg/mL	KL4 ^c	5.8	175	6

^aNeed for repeat surfactant doses is based on continuing signs and symptoms of respiratory distress as well as an oxygen requirement (fraction of inspired oxygen [F_{iO_2}]) of greater than 30%–40%.

^bNo longer commercially available in the United States; included for historical perspective.

^c21-amino acid peptide that mimics SP-B.

DPPC = dipalmitoyl phosphatidylcholine; POPG = palmitoyloleyl phosphatidylglycerol; PG = phosphatidylglycerol; SP-B = surfactant protein B; SP-C = surfactant protein C.

- c. Comparison of surfactant products: Clinical outcomes
 - i. Natural versus synthetic products
 - (a) Natural products result in improved outcomes compared with historical synthetic product (i.e., colfosceril).
 - (b) A reduction in RDS-related deaths was observed at 14 days with lucinactant compared with beractant; a longer-term benefit has not been shown. No difference in morbidities associated with prematurity (e.g., BPD).
 - (c) No difference in short- or long-term outcomes when comparing lucinactant with poractant
 - ii. Natural product comparison
 - (a) A short-term clinical benefit (e.g., reduced oxygen requirement, faster wean of mechanical ventilation, decreased need for repeat doses) was observed with calfactant compared with beractant. No difference in incidence of BPD or mortality.
 - (b) Meta-analysis comparing poractant with beractant showed that risk of death or need for oxygen at 36 weeks' postmenstrual age was reduced in group receiving higher initial poractant dose (i.e., greater than 100 mg/kg).
 - (c) No comparison studies of calfactant with poractant
 - (d) The American Academy of Pediatrics (AAP) concluded that it is unclear whether there is a significant difference in clinical outcomes when comparing the natural products.
- d. Prophylaxis versus rescue surfactant administration
 - i. Prophylaxis
 - (a) Surfactant administration to neonates at high risk of RDS to prevent rather than treat RDS.
 - (b) Surfactant administration occurs in the delivery room before the onset of RDS, typically within 10–30 minutes after birth; theoretically, the ideal timing would be before the neonate's first breath or before positive pressure ventilation is administered.
 - (c) May result in administration to more neonates than would actually develop RDS.
 - ii. Rescue
 - (a) Surfactant administration to neonates with established RDS for treatment
 - (b) "Early" rescue surfactant therapy is administered within 1–2 hours after birth.
 - (c) "Delayed" or "late" rescue surfactant therapy is administered 2 hours or more after birth, typically within 12 hours.
 - iii. Prophylactic surfactant administration does not result in clinically important benefits (e.g., reduced mortality or incidence of BPD) compared with continuous positive airway pressure (CPAP) provided in the delivery room and followed by rescue surfactant, if indicated (about one-third did not require rescue surfactant).
 - iv. Early rescue treatment decreases the risk of mortality and chronic lung disease compared with delayed treatment.
- e. Administration techniques
 - i. Surfactant may be administered to neonates who are intubated and mechanically ventilated, and to those who are not intubated.
 - (a) INSURE (acronym) method of surfactant administration: **I**ntubation, **s**urfactant administration, **e**xtubation to CPAP
 - (b) Less invasive surfactant administration (LISA)/minimally invasive surfactant therapy (MIST) uses a thin catheter for intratracheal surfactant administration to neonates on CPAP: Shown to reduce need for mechanical ventilation and BPD compared to INSURE.
 - ii. The neonate is positioned to facilitate uniform delivery of surfactant to all lung fields.
 - (a) For example, the surfactant dose is divided into four aliquots and delivered to the neonate in four different positions: (1) body tilted slightly downward with the head turned to the right, (2) body tilted slightly downward with the head turned to the left, (3) body tilted

- slightly upward with the head turned to the right, (4) body tilted slightly upward with the head turned to the left.
- (b) Adequate distribution may also occur with delivery in two aliquots: (1) body tilted and head turned to the right and (2) body tilted and head turned to the left.
- f. Adverse effects
 - i. Apnea, bradycardia, oxygen desaturation
 - ii. Pneumothorax may occur because of a rapid increase in lung compliance if changes to mechanical ventilation settings are not made quickly.
 - iii. Pulmonary hemorrhage rarely occurs, but it is most common in extremely low-birth-weight neonates.
- 2. Other preventive and treatment strategies
 - a. Antenatal corticosteroid
 - i. Betamethasone 12 mg intramuscularly every 24 hours for two doses administered to women in preterm labor (between 24 and 34 weeks' gestation)
 - (a) Delivery should be delayed for at least 24 hours for improved response; benefit lasts up to 7 days.
 - (b) Dexamethasone 6 mg intramuscularly every 12 hours for four doses is an alternative regimen.
 - (c) If preterm delivery is delayed, the benefit of repeated courses is controversial.
 - ii. Promotes fetal lung maturation and surfactant production
 - iii. Significantly reduces mortality and incidence of RDS; effect is additive with surfactant therapy.
 - b. Inhaled nitric oxide
 - i. Theorized role in RDS
 - (a) Intrapulmonary shunting of blood owing to ventilation-perfusion mismatching or extrapulmonary shunting owing to pulmonary hypertension can worsen RDS.
 - (b) Inhaled nitric oxide may improve oxygenation by vasodilating the pulmonary vasculature, thus lowering pulmonary vascular resistance and improving distribution of pulmonary blood flow.
 - ii. Summary of trials and meta-analysis
 - (a) Three meta-analyses, including a Cochrane review, evaluated the use of inhaled nitric oxide in neonates with RDS.
 - (b) No difference in mortality or incidence of BPD was shown.
 - (c) Inhaled nitric oxide cannot be recommended for routine treatment of preterm neonates with RDS.

II. BRONCHOPULMONARY DYSPLASIA

A. Background

1. Also known as chronic lung disease
2. Significant risk of mortality and long-term morbidity
3. Definition: "Old" versus "new" BPD
 - a. Originally described by Northway in 1967; mean gestational age of the study cohort was 33 weeks with a birth weight of 1600 g.
 - i. "Old BPD": Oxygen dependence for longer than 28 days in the presence of characteristic chest radiograph findings
 - ii. Radiographic findings: Heterogeneous pattern of small airway obstruction, emphysema, atelectasis, hyperinflation and cystic disease

- b. In 1999, Jobe described the “new BPD” in a cohort of neonates with a mean gestational age of 27 weeks and birth weight less than 1000 g.
 - i. “New BPD”: Initially described as the need for supplemental oxygen at or beyond 36 weeks’ postmenstrual age; broken down into 3 classifications.
 - (a) Mild: Period of oxygen requirement of at least 28 days, but on room air by 36 weeks’ postmenstrual age
 - (b) Moderate: Continued oxygen requirement with a fraction of inspired oxygen (FiO₂) less than 30%
 - (c) Severe: Continued oxygen requirement with an FiO₂ of at least 30% or any form of positive pressure ventilation or CPAP pressure
 - ii. Radiographic findings: Homogeneous, diffuse lung parenchymal disease with fewer and larger alveolar spaces, decreased vascularization, and decreased surface area
 4. Risk factors
 - a. Premature birth
 - b. Very low (less than 1500 g) and especially extremely low (less than 1000 g) birth weight
 - c. Invasive mechanical ventilation resulting in barotrauma and volutrauma
 - d. Others including chorioamnionitis, airway colonization with *Ureaplasma urealyticum*, pulmonary edema, persistent patent ductus arteriosus, poor nutrition
- B. Clinical Presentation
1. Tachypnea, retractions, shallow breathing, wheezing, increased oxygen requirement, and bronchospasm may be present.
 2. Chest radiograph typically appears diffusely hazy with areas of lung hyperinflation and hypoinflation (i.e., “patchy atelectasis”).

Patient Case

2. The patient in case 1 had a modest response after two doses of surfactant, but he remains intubated and mechanically ventilated, requiring 30% oxygen 24 hours after birth. Because of his prematurity and continued need for invasive respiratory support, the medical team would like to initiate a therapy to prevent the development of BPD. Which medication would be best to recommend?
 - A. Azithromycin
 - B. Caffeine
 - C. Dexamethasone
 - D. Poractant

C. Prevention

1. Caffeine: Caffeine for Apnea of Prematurity (CAP) trial showed a reduced incidence of BPD (defined as need for supplemental oxygen at 36 weeks’ postmenstrual age) in neonates receiving caffeine compared with placebo.
2. Vitamin A
 - a. 5000 units administered intramuscularly three times a week for 4 weeks to neonates with a birth weight less than 1000 g has been shown to decrease the risk of BPD; oral administration did not result in the same benefit.
 - b. A long-term follow-up trial did not show a difference in neurodevelopmental outcomes between neonates who received vitamin A compared with placebo.

-
- c. A 2016 Cochrane review concluded that vitamin A supplementation modestly reduced BPD among very-low-birth-weight neonates. The authors concluded that the decision to use vitamin A should be based on the local incidence of BPD and weighed against the lack of other proven benefits (e.g., neurodevelopmental outcomes).
 3. Inhaled nitric oxide
 - a. Animal models suggest that inhaled nitric oxide decreases lung inflammation, improves surfactant function, and augments lung growth.
 - b. Clinical trials of preterm human neonates have failed to show a reduction in the incidence or severity of BPD.
 4. Antenatal corticosteroids: Although shown to decrease the incidence of RDS, there is no evidence of a reduced risk of BPD, which may be owing to improved survival of very preterm neonates.
 5. Postnatal corticosteroids
 - a. Early (less than 96 hours after birth) and moderately early (7–14 days of age) systemic dexamethasone have been shown to significantly decrease the incidence of BPD; this practice was common in the 1990s.
 - b. In the early 2000s, AAP advised against the use of postnatal corticosteroids for the prevention of BPD because of evidence of significant long-term neurologic complications (e.g., increased cerebral palsy and developmental delay).
 - i. Most commonly, high doses (0.5 mg/kg/day) of dexamethasone for long durations (up to 42 days) were used in these studies.
 - ii. A 2017 Cochrane Review concluded the use of dexamethasone regardless of timing of initiation, dose, or duration is still not supported by currently published evidence.
 - c. Clinicians are still using lower-dose (less than 0.2 mg/kg/day) postnatal corticosteroids in chronically mechanically ventilated neonates to facilitate extubation.
 - i. Adverse neurodevelopmental outcomes have not been reported for this lower-dose regimen when used after a few weeks of age.
 - ii. However, the optimal dosing and timing, as well as the overall safety and effectiveness in preventing BPD, of this intervention are unknown. Clinical trials to address this question are ongoing and encouraged by AAP.
 - d. Hydrocortisone has also been evaluated for the prevention of BPD.
 - i. Some evidence suggests low-dose (1 mg/kg/day) hydrocortisone tapered over the first 10 days to 2 weeks after birth reduces the incidence of BPD without affecting neurodevelopment.
 - (a) The most benefit may be in neonates exposed to prenatal inflammation (e.g., chorioamnionitis).
 - (b) Concurrent use of systemic corticosteroids with indomethacin/ibuprofen may increase the risk of spontaneous intestinal perforation.
 - ii. Higher doses (3–6 mg/kg/day) after the first week of age have not been shown to decrease the incidence of BPD.
 - e. Inhaled budesonide: A 2017 Cochrane review concluded that data are insufficient to recommend inhaled corticosteroids for BPD prevention in preterm neonates.
 6. Surfactant
 - a. Not shown to reduce BPD; may be because of increased survival of very preterm neonates.
 - b. Late administration to preterm neonates who remain intubated at 14 days may improve pulmonary outcomes (e.g., reduced rehospitalizations) at 1 year of age.
 7. Indomethacin/ibuprofen
 - a. It was theorized that preventing the PDA, a risk factor for BPD, would decrease the incidence of BPD.
 - b. Trials of prophylactic closure of the ductus arteriosus have not shown a decrease in the incidence of BPD.
-

8. Macrolide therapy
 - a. *U. urealyticum* has been isolated from the respiratory tract of neonates with BPD.
 - b. Most studies evaluating the effect of macrolide antibiotics in neonates with *Ureaplasma*-positive respiratory cultures have shown clearance of the organism but no effect on incidence of BPD; one study evaluating clarithromycin found a reduction in the incidence of BPD.
 - c. Macrolide antibiotics administered to all neonates at high risk of developing BPD did not prevent BPD; in a subset analysis of neonates with positive PCR for *Ureaplasma*, azithromycin initiated within 3 days of age and continued for up to 6 weeks decreased the incidence of BPD.
 - d. The routine use of macrolides for the prevention of BPD caused by *Ureaplasma* colonization/infection is not recommended because of very limited evidence of a beneficial effect.

Patient Case

3. The patient from cases 1 and 2 is now 36 weeks' postmenstrual age. During his NICU stay, he was treated for RDS and *Klebsiella* sepsis. He has had several failed extubation attempts and remains intubated, requiring 30%–40% oxygen to maintain adequate oxygenation and prevent frequent desaturations. His chest radiograph reveals diffuse haziness with lung hyperinflation consistent with chronic lung disease. Which treatment for his severe BPD is best supported by the literature?
 - A. Albuterol 2 puffs by endotracheal tube every 6 hours, budesonide 0.25 mg by nebulizer every 12 hours, and furosemide 2 mg/kg/dose orally daily.
 - B. Albuterol 2 puffs by endotracheal tube every 6 hours, budesonide 0.25 mg by nebulizer every 12 hours, and hydrochlorothiazide/spironolactone 3 mg/kg/day by mouth divided every 12 hours.
 - C. Albuterol 2 puffs by endotracheal tube every 6 hours and fluticasone 2 puffs by endotracheal tube every 12 hours.
 - D. Albuterol 2 puffs by endotracheal tube every 6 hours as needed for bronchospasm and furosemide 1 mg/kg/dose intravenously as needed for signs of pulmonary fluid overload.

D. Treatment

1. Diuretics
 - a. Thiazide diuretics (e.g., hydrochlorothiazide), potassium-sparing diuretics (e.g., spironolactone), and loop diuretics (e.g., furosemide) are commonly used in clinical practice to decrease pulmonary edema in patients with BPD.
 - b. Short-term benefits of improved oxygenation and lung compliance have not been shown to correspond to improvements in long-term outcomes (e.g., decreased need for mechanical ventilation, length of hospital stay, or mortality).
 - c. Electrolyte derangements are common and can lead to complications such as nephrocalcinosis and osteopenia caused by increased urinary calcium loss.
 - i. Thiazides may have calciuric effects similar to loop diuretics in preterm neonates.
 - ii. Hypochloremia may be associated with a poorer outcome in infants with BPD.
 - iii. Various alterations to the diuretic regimen (e.g., administration by inhalation, every-other-day dosing) have been studied in an effort to minimize adverse effects. Although some have shown fewer electrolyte abnormalities, a lack of long-term clinical benefit remained.
 - d. Chronic use of diuretics should be discouraged because of the very limited evidence with respect to meaningful benefits, together with the potential for significant adverse effects.
2. Bronchodilators
 - a. β -Agonists have been shown to improve lung compliance and decrease pulmonary resistance.
 - b. They may be beneficial in the management of acute exacerbations of BPD to improve airway hyperactivity, although this is not a significant component of the pathophysiology of "new BPD".

- c. Most reports of bronchodilator use in BPD are single-dose studies or short-term evaluations; long-term effects have not been well studied, and there is no evidence of reduced need for ventilator support or mortality.
- 3. Corticosteroids
 - a. Systemic corticosteroids: Adverse effects outweigh potential benefits.
 - b. Inhaled corticosteroids
 - i. Inhaled corticosteroids have the theoretical advantage of decreased systemic adverse effects compared with systemic corticosteroids; however, trials have not confirmed this.
 - ii. There is no evidence to support long-term clinical benefits, so routine use is not recommended.

III. APNEA OF PREMATURITY

A. Background

- 1. An immature central respiratory drive, inability to maintain airway patency, and underdeveloped respiratory muscles cause hypoventilation resulting in apneic and cyanotic spells.
- 2. Types
 - a. Central: Reduced sensitivity to hypercarbia of the central respiratory center results in a lack of respiratory effort.
 - b. Obstructive: A respiratory effort exists, as evidenced by chest wall movement, but the inability to maintain upper airway (i.e., larynx and pharynx) patency results in obstruction of airflow.
 - c. Mixed: The most common type of apnea of prematurity, a combination of central and obstructive apnea
- 3. Other causes of apnea in a neonate
 - a. Sepsis
 - b. Necrotizing enterocolitis
 - c. Gastroesophageal reflux
 - d. Seizures
 - e. IVH
 - f. Drugs (i.e., respiratory depressants, alprostadil)
 - g. Inborn errors of metabolism
 - h. Central nervous system (CNS) structural abnormalities

B. Clinical Presentation

- 1. Cessation of breathing for at least 20 seconds or pauses in breathing of less than 20 seconds if associated with bradycardia (heart rate less than 100 beats/minute), cyanosis, or pallor
- 2. Diagnosis of exclusion: Other causes of apnea must be ruled out.
- 3. Risk factors
 - a. Prematurity
 - i. The incidence of apnea is inversely related to gestational age.
 - ii. The incidence of apnea is significantly lower if the gestational age is older than 34 weeks.
 - b. Extremely low birth weight (less than 1000 g)

Patient Case

4. The patient in cases 1–3 is now 37-3/7 weeks' postmenstrual age. After prolonged intubation and mechanical ventilation, he was extubated 10 days ago to nasal CPAP with 21% oxygen. He has received caffeine since shortly after birth but has had no apneic spells since extubation. Which is the best recommendation regarding his methylxanthine therapy?
- A. Discontinue caffeine, and monitor the patient for apnea recurrence.
 - B. Taper the caffeine dose over the next 2 weeks, and discontinue it if no apnea occurs during the taper.
 - C. Switch to theophylline because its shorter half-life will allow for a faster wean off therapy.
 - D. Continue caffeine until discharge, and then plan to taper off over several weeks as an outpatient.

C. Treatment

- 1. Methylxanthines (i.e., theophylline/aminophylline and caffeine)
 - a. Mechanism of action: Nonspecific inhibitor of adenosine receptors
 - i. CNS stimulant
 - ii. Increase respiratory drive
 - iii. Increase sensitivity to hypercapnia
 - iv. Increase diaphragmatic contractility
 - b. Comparison of available agents – caffeine citrate is preferred over theophylline in clinical practice
 - i. Pharmacokinetics
 - (a) Distribution: Theophylline has a higher free fraction in neonates than in older children and adults because of reduced plasma protein binding.
 - (b) Metabolism
 - (1) Oxidation and *N*-demethylation of theophylline is decreased in neonates compared with adults because of the immaturity of the hepatic enzyme system.
 - (2) Theophylline is methylated to caffeine.
 - (3) Demethylation of caffeine is decreased in neonates compared with adults.
 - (c) Elimination
 - (1) Theophylline (24–36 hours) has a relatively short half-life compared with caffeine (72–100 hours).
 - (2) In neonates, theophylline (55%) and caffeine (85%) are primarily excreted unchanged in the urine.
 - ii. Efficacy
 - (a) Theophylline and caffeine have similar efficacy in treating apnea of prematurity.
 - (b) A randomized controlled trial suggests that caffeine, but not theophylline, is beneficial for preventing apnea.
 - (c) Dosing

Table 2. Dosing Recommendations for Methylxanthines

Drug	Route	Loading Dose (mg/kg)	Maintenance Dose (mg/kg/dose)	Dosing Interval (hours)
Theophylline	Oral	5–6	1–2	8–12
Aminophylline	IV	6–8	1–2	8–12
Caffeine citrate	Oral, IV	20	5–10	24

IV = intravenous.

- iii. Safety
 - (a) Theophylline is associated with increased adverse effects, including tachycardia, feeding intolerance, irritability, jitteriness, and seizures.
 - (b) Similar adverse effects can occur with caffeine, but they are relatively uncommon because of its wider therapeutic index compared with theophylline.
 - iv. Monitoring
 - (a) Clinical response (i.e., reduced number of apneic episodes) is the most useful monitoring value for efficacy.
 - (b) The therapeutic range of theophylline serum concentrations is considered 5–12 mcg/mL; theophylline concentrations should be routinely monitored during therapy because of theophylline's narrow therapeutic index.
 - (c) Serum concentrations of caffeine are not shown to correlate well with efficacy or toxicity, so routine monitoring is not recommended.
 - v. Clinical practice: The wide therapeutic index and longer half-life allowing for once-daily administration make caffeine the therapy of choice.
2. Association with gastroesophageal reflux
 - a. Considerable controversy exists regarding whether reflux worsens apnea of prematurity and whether methylxanthine therapy worsens reflux.
 - b. Most evidence suggests that treatment of gastroesophageal reflux does not reduce or resolve apneic episodes.
 3. CAP trial: Multicenter randomized placebo-controlled trial of caffeine versus placebo in neonates with apnea of prematurity
 - a. Short-term outcomes in caffeine treatment group
 - i. These were the secondary end points of the study.
 - ii. Decreased duration of respiratory support (i.e., positive airway pressure, supplemental oxygen)
 - iii. Decreased rates of BPD
 - iv. No difference in NEC or IVH
 - v. Temporary reduction in weight gain during first 3 weeks of treatment
 - vi. Effects most significant when caffeine is initiated within 3 days of birth.
 - b. Long-term neurodevelopmental outcomes
 - i. These were the primary end points of the study.
 - ii. Significantly lower incidence of death or survival with a neurodevelopmental disability at 18–21 months of age; there was no difference between groups at 5-year follow-up.
 4. Treatment duration
 - a. Most neonates will “outgrow” apnea of prematurity by 34–36 weeks' postmenstrual age because of maturation of the central respiratory center, so methylxanthine therapy can be discontinued at that time.
 - b. Most clinicians will monitor the neonate for up to 1 week after discontinuation of methylxanthine therapy to ensure that the drug has been eliminated from the body and that apnea of prematurity has resolved before discharging the patient home.

IV. INTRAVENTRICULAR HEMORRHAGE

A. Background

1. Mechanism of hemorrhage
 - a. Likely multifactorial
 - b. Lack of cerebral pressure autoregulation resulting in an inability to maintain relatively steady cerebral blood flow at a range of cerebral perfusion pressures
 - i. Factors causing low cerebral blood flow: Hypotension, perinatal asphyxia
 - ii. Factors causing increased cerebral blood flow: Hypertension, rapid infusion of fluid bolus, vasopressor therapy, pain, handling, hypercarbia
 - iii. Factors causing elevated cerebral venous pressure: RDS, pneumothorax, pulmonary hemorrhage, positive pressure ventilation
 - iv. Fluctuating cerebral blood flow is common in ventilated neonates who are out of synchrony with the ventilator.
 - c. Excessive angiogenesis within the germinal matrix: VEGF (vascular endothelial growth factor) is a potent angiogenic factor
 - d. Cytokines induce cyclooxygenase-2 production resulting in increased prostaglandin production, which causes vasodilatation that further affects cerebral pressure autoregulation.
2. Grades
 - a. Grade I: Hemorrhage is limited to the germinal matrix.
 - b. Grade II: Hemorrhage in the lateral ventricle, blood fills less than 50% of the ventricle.
 - c. Grade III: Hemorrhage in the lateral ventricle causing distension, blood fills more than 50% of the ventricle.
 - d. Grade IV: Hemorrhage into the surrounding parenchyma
3. Complications
 - a. Periventricular leukomalacia
 - b. Posthemorrhagic hydrocephalus: Up to 40% will require a ventriculoperitoneal shunt
 - c. Cerebral palsy and/or mental retardation
 - i. The risk for neonates with grade I or II IVH is similar to that for a premature neonate with a normal cranial ultrasonography and similar NICU course (i.e., experienced similar complications of prematurity).
 - ii. Neonates with grade III or IV IVH have a 35%–50% and 75% increased risk of neurodevelopmental sequelae, respectively.

B. Clinical Presentation

1. Symptoms
 - a. Often asymptomatic: Up to 50% of cases
 - b. Symptoms may include rapid decline in hematocrit, acidosis, hypo- or hyperglycemia, bulging fontanelle, altered consciousness, seizures, and cardiorespiratory deterioration.
2. Diagnosed by cranial ultrasonography
 - a. 50% occur on the first day of life.
 - b. 90% occur within the first 4 days of life.
3. Risk factors
 - a. Birth weight: Lower birth weights correlate with a higher incidence of IVH.
 - b. Premature birth

C. Prevention

1. Antenatal corticosteroids
 - a. Betamethasone or dexamethasone
 - b. Although their primary indication is to promote fetal lung maturation, antenatal corticosteroids also have been shown to reduce the risk of IVH.
2. Indomethacin
 - a. Proposed mechanism: Cyclooxygenase-1 and -2 inhibition reduces prostaglandin production, thus decreasing cerebral blood flow; also can stimulate vascular maturation and is an antioxidant.
 - b. Regimen: 0.1 mg/kg/dose intravenously every 24 hours for 3 doses; administered within 6–12 hours of life to neonates with a birth weight less than 1000–1250 g
 - c. Significantly reduces the incidence of severe (grade III and IV) IVH.
 - i. Benefit not shown with ibuprofen prophylaxis.
 - ii. Also shown to reduce the risk of symptomatic PDA.
 - d. Not shown to improve long-term survival without neurodevelopmental sequelae.
3. Recombinant human erythropoietin
 - a. Proposed mechanism: Neuroprotection after brain injury (e.g., hypoxic-ischemic encephalopathy, caused by premature birth) is facilitated by anti-inflammatory, anti-excitotoxic, antioxidant, and anti-apoptotic effects on neurons and oligodendrocytes, which promote neurogenesis and angiogenesis.
 - b. High-dose regimens (1000–30,000 units/kg/dose), much higher than those previously used for anemia of prematurity, are required to achieve measurable concentrations within the brain.
 - c. A 2020 study showed no difference in death or severe neurodevelopmental impairment at 2 years of age between high-dose erythropoietin and placebo.

V. PATENT DUCTUS ARTERIOSUS**A. Background**

1. The ductus arteriosus is a vessel connecting the pulmonary artery to the aorta that allows blood flow to bypass the fetal lungs.
2. Decreased circulating prostaglandin concentrations and increased oxygen levels promote postnatal constriction of the ductus arteriosus; therefore, the failure of circulating prostaglandin concentrations to drop results in persistent patency of the ductus arteriosus.
3. Ductal constriction typically occurs within 72 hours of birth in term neonates and by 4 days in preterm neonates born older than 29 weeks' gestation.

B. Clinical Presentation

1. Symptoms: Murmur, hyperactive precordium, bounding pulses, widened pulse pressure, hypotension, worsening respiratory status
2. Diagnosis is confirmed by echocardiogram.
3. Risk factors
 - a. Gestational age: 70%–80% of neonates born before 28 weeks' gestation will have a PDA.
 - b. Lack of antenatal corticosteroids
 - c. RDS
4. Complications
 - a. "Ductal steal" results in a left-to-right shunt of blood that reduces blood flow to some major organs (e.g., poor kidney perfusion can result in elevated serum creatinine/acute kidney injury) and increases pulmonary blood flow excessively.
 - b. Hypotension, pulmonary hemorrhage, NEC, IVH, pulmonary edema, prolonged need for mechanical ventilation, BPD, and heart failure are associated with the failure of ductal closure.

Patient Case

5. A 750-g girl was delivered prematurely at 26 weeks' gestational age due to maternal chorioamnionitis. Soon after birth, she had symptoms of RDS and subsequently received two doses of surfactant. Despite some improvement in her symptoms, she remained intubated and mechanically ventilated. Caffeine was initiated. She also received three doses of indomethacin according to the NICU's IVH prophylaxis protocol. At 12 days of age, she became tachycardic and had a widened pulse pressure; also, a systolic murmur was heard. She became hypotensive, so a dopamine continuous infusion was initiated, and the dose was titrated to 20 mcg/kg/minute. Her total daily fluid intake was 120 mL/kg/day. Her chest radiograph revealed pulmonary edema, and her ventilator support had to be increased. An echocardiogram (ECHO) was ordered, which showed a moderate PDA with left-to-right shunting. Which is the best therapy to recommend for the management of this patient's PDA?
- Acetaminophen 15 mg/kg/dose intravenously every 6 hours for 3 days because indomethacin failed.
 - Furosemide 1 mg/kg/dose intravenously every 12 hours until pulmonary edema is resolved; then recheck ECHO.
 - Indomethacin 0.2 mg/kg/dose for 1 dose; then 0.25 mg/kg/dose every 12 hours for 2 doses for late symptomatic treatment.
 - Restrict fluid intake to 100 mL/kg/day, and recheck ECHO in 2 days.

C. Treatment

- Supportive care, including fluid restriction and respiratory support, may be sufficient to manage the symptoms of PDA until spontaneous closure occurs, especially in neonates born older than 28 weeks' gestation.
- Pharmacologic agents for closure of PDA

Table 3. Drugs to Promote Closure of the PDA

Drug	MOA	Regimen	Adverse Effects	Comments
Indomethacin	Reduced prostaglandin synthesis by inhibition of cyclooxygenase site on the PGHS complex	- Dependent on PNA - IV: Initial dose 0.2 mg/kg/dose, followed by 0.1–0.25 mg/kg/dose every 12–24 hours for two more doses - Adjustment of dosing interval for urine output: - If > 0.6 but < 1 mL/kg/hr, every 24 hr - If < 0.6 mL/kg/hr, hold dose	- Renal dysfunction - NEC - SIP - GI bleed	- Efficacy ~70% - Efficacy decreases with increasing PNA - Infusing the dose over 20–30 minutes (vs. bolus over a few minutes) may diminish the negative effect on cerebral and mesenteric blood flow

Table 3. Drugs to Promote Closure of the PDA (*continued*)

Drug	MOA	Regimen	Adverse Effects	Comments
Ibuprofen	Reduced prostaglandin synthesis by inhibition of cyclooxygenase site on the PGHS complex	• IV/PO: 10 mg/kg/dose for one dose; then 5 mg/kg/dose for two doses given at 24 and 48 hours after the initial dose • Hold dose if urine output is < 0.6 mL/kg/hr	• Similar to indomethacin, but incidence may be lower because of reduced effect on mesenteric and renal blood flow	• Efficacy ~70%
Acetaminophen	Reduced prostaglandin synthesis by inhibition of peroxidase site on the PGHS complex	• IV, PO: 15 mg/kg/dose every 6 hours for 2–7 days	• Concern for hepatotoxicity, although not reported in the small case series or trials published so far; there have been reports of elevated transaminases	• Limited efficacy and safety data available • May be useful in neonates with contraindications to indomethacin/ibuprofen or whose therapies have failed

IV = intravenously; MOA = mechanism of action; NEC = necrotizing enterocolitis; PGHS = prostaglandin H₂ synthase enzyme; PNA = postnatal age; PO = orally; SIP = spontaneous intestinal perforation.

3. Optimal timing for initiating pharmacologic treatment of a PDA is controversial.
 - a. Early (less than 3 days old) versus late (7–14 days old) symptomatic treatment
 - i. Studies from the 1980s and early 1990s suggest a reduction in the need for mechanical ventilation, surgical ligation of the PDA and BPD with early indomethacin treatment of the PDA.
 - (a) The lack of routine antenatal corticosteroid use and exogenous surfactant replacement during this time may have affected the results.
 - (b) Outcomes have not been well studied since antenatal corticosteroids, surfactant, and non-invasive modes of respiratory support have become routine interventions for premature neonates.
 - ii. Closure rates with early treatment are high; however, this practice may subject more neonates to unnecessary medication and adverse effects because their PDA could have closed spontaneously.
 - iii. More recently, a difference in long-term benefits (e.g., reduction in BPD or NEC, improved survival) has not been clearly shown when early treatment is compared with delayed treatment.
 - b. Late/delayed symptomatic treatment
 - i. Early fluid restriction (typically to 120 mL/kg/day or less) may delay or negate the need for pharmacologic treatment of the PDA.
 - ii. Sick neonates with a hemodynamically significant PDA have often been excluded from trials of late treatment, so their ability to tolerate this approach or its effects on long-term outcomes are unknown.
 - iii. The outcome of treatment delays beyond 14 days has not been studied.

4. Repeat courses
 - a. Response rate after a second course of indomethacin or ibuprofen is around 40%.
 - b. Lowest rates of closure occur in the most premature neonates.
 - c. It is unknown whether several courses of indomethacin/ibuprofen increase the risk of adverse effects.
 5. Monitoring
 - a. Renal function (i.e., serum creatinine and urine output)
 - b. Platelet count
 - c. Liver function tests: With use of acetaminophen
 - d. Gastrointestinal (GI) signs (e.g., bloody stool; distended, discolored abdomen): Risk of spontaneous intestinal perforation may be higher if given during first week of life, with hypotension, or with concurrent corticosteroids.
 - e. Serum concentrations
 - i. Not routinely done at most institutions.
 - ii. Studies from a few institutions report improved closure rates with individualized dosing based on serum concentrations of indomethacin.
 6. Surgical closure: Considered if urgent closure indicated or if there are contraindications to pharmacologic treatment (e.g., NEC, GI perforation, pulmonary hemorrhage) or when pharmacologic treatment courses have failed.
- D. Prevention
1. Indomethacin
 - a. Regimen: 0.1 mg/kg/dose intravenously every 24 hours for three doses given within 6–12 hours of birth to neonates with birth weights less than 1000–1250 g
 - b. Shown to reduce the incidence of symptomatic PDA.
 - c. Not shown to increase survival or reduce long-term neurodevelopmental disability.
 - d. May result in unnecessary exposure to indomethacin as up to 60% of PDAs present within 1 day of birth will close spontaneously.
 2. Ibuprofen
 - a. Regimen: 10 mg/kg/dose x 1 dose within 6–24 hours of birth followed by 5 mg/kg/dose x 2 doses given 24 and 48 hours after first dose
 - b. Shown to reduce incidence of PDA and need for rescue treatment or surgical ligation
 - c. Not shown to reduce mortality, IVH, or BPD
 3. Acetaminophen: Not well studied for prevention of PDA

VI. NECROTIZING ENTEROCOLITIS

- A. Background
1. Pathogenesis is multifactorial.
 - a. Immaturity of the GI tract is the most important factor.
 - i. Immaturity results in intestinal hyperpermeability.
 - ii. Decreased peristalsis increases the time intestinal bacteria are in contact with carbohydrate substrates from feedings and increases the time the bowel is exposed to bacterial antigens, thus increasing inflammation.
 - iii. Decreased immunoglobulin A (IgA) production by the immature intestine compromises an important protective mechanism against pathogens.
 - b. It is thought that an exaggerated inflammatory response occurs after the exposure of bacterial pathogens, which colonize the gut, to a substrate provided by enteral feedings.

- c. A perinatal hypoxic-ischemic episode preceding NEC may be the inciting event in some cases; however, this is unlikely to be the overall primary cause because the age of onset for NEC, about 21 days in preterm neonates, is remote from birth, and no such event is identifiable in many cases of NEC.
 - d. Necrosis usually involves the ileum and proximal colon.
2. Risk factors
- a. Premature birth
 - i. Incidence is inversely related to gestational age.
 - ii. Unlikely in term neonates except for those with specific risk factors that decrease mesenteric blood supply (e.g., congenital heart disease, sepsis, hypotension).
 - b. Very low (less than 1500 g) or extremely low (less than 1000 g) birth weight
 - c. Formula feeding (as opposed to breast milk)
 - d. Abnormal bacterial colonization of the intestinal tract because of prolonged antibiotic exposure or acid-suppressive therapy
 - i. Decreased normal gut flora
 - ii. Proliferation of pathogenic bacteria
- B. Clinical Presentation
- 1. Often non-specific signs, including apnea, bradycardia, lethargy, temperature instability
 - 2. GI signs include feeding intolerance (e.g., gastric residuals or emesis), abdominal distension, bloody stool, discoloration of abdominal wall.
 - 3. Radiologic findings include dilated loops of bowel, pneumatosis intestinalis (hallmark sign of NEC), portal venous gas, and pneumoperitoneum (indicates intestinal perforation).
 - 4. Mortality is high (up to 30% overall), especially with fulminant NEC (more than 90%).
 - a. In survivors, significant GI morbidities occur, including intestinal failure (e.g., short bowel syndrome) leading to nutrient malabsorption and failure to thrive, stricture formation, and complications of long-term parenteral nutrition, including cholestasis and liver failure.
 - b. Survivors also have significant neurologic complications, including neurodevelopmental delay and cerebral palsy.
 - 5. Modified Bell's staging criteria

Table 4. Modified Bell's Staging Criteria for NEC

Stage	Systemic and Laboratory Findings	Abdominal Findings	Radiologic Findings
Ia – suspected NEC	Temperature instability, apnea, bradycardia	Feeding intolerance, mild abdominal distension, occult bloody stool	Typically normal or mildly dilated bowels
Ib – suspected NEC	Same as stage Ia	Grossly bloody stool	Same as stage Ia
IIa – definite NEC, mildly ill	Same as stage Ia	Same as stage I with lack of bowel sounds, possible abdominal tenderness	Pneumatosis intestinalis, ileus
IIb – definite NEC, moderately ill	Same as stage Ia with mild metabolic acidosis, mild thrombocytopenia	Same as stage I with peritonitis, definite abdominal tenderness, right lower quadrant mass	Same as stage IIa and possible portal venous gas, with or without ascites

Table 4. Modified Bell's Staging Criteria for NEC (*continued*)

Stage	Systemic and Laboratory Findings	Abdominal Findings	Radiologic Findings
IIIa – advanced NEC, severely ill, intact bowel	Same as stage IIb with hypotension, apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, neutropenia	Same as stage IIb with marked abdominal tenderness and distension	Same as stage IIb with definite ascites
IIIb – advanced NEC, severely ill, perforated bowel	Same as stage IIIa	Same as stage IIIa	Same as IIIa with pneumoperitoneum

Patient Case

6. The patient in case 5 who was born at 26 weeks' gestational age was treated for a PDA with indomethacin at 12 days of age; a repeat ECHO confirmed closure. Trophic enteral feedings were discontinued when the PDA was diagnosed. Feedings were resumed at 14 days of age with 2 mL every 3 hours (20 mL/kg/day) of preterm formula at 24 kcal/oz. Feedings were advanced by 20 mL/kg every day. At 20 days of age, she developed abdominal distension, bloody stools, and temperature instability. Her feedings were discontinued. An urgent abdominal radiograph was ordered, which revealed dilated loops of bowel and pneumatosis intestinalis with evidence of free air. Which is the best antibiotic regimen to recommend?

- A. Ampicillin plus gentamicin
- B. Ampicillin plus gentamicin plus metronidazole
- C. Piperacillin/tazobactam plus metronidazole
- D. Vancomycin plus imipenem

C. Treatment

1. Nonpharmacologic

- a. Bowel rest and abdominal decompression with gastric tube
- b. Peritoneal drains and/or surgery
 - i. Indicated if bowel perforation occurs.
 - ii. Mortality higher if surgery is required.

2. Pharmacologic

- a. Supportive care
 - i. Intravenous fluids/parenteral nutrition
 - (a) Third spacing often increases fluid requirements to 1.5 times maintenance amounts.
 - (b) Fluid loss from gastric output requires intravenous fluid replacement.
 - ii. Vasopressors
- b. Antibiotics
 - i. The goals are to prevent ongoing GI mucosal injury, prevent translocation of enteric bacteria into the bloodstream, and reduce mortality.
 - ii. Common pathogens
 - (a) Blood cultures are positive in only around 30% of neonates with NEC.
 - (b) Enterobacteriaceae (e.g., *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.) are the most common causative organisms.

- (c) *Staphylococcus epidermidis*, *Enterococcus* spp., *Staphylococcus aureus*, *Clostridium perfringens*, *Pseudomonas aeruginosa*, and *Salmonella* have also been isolated from neonates with NEC.

- iii. Possible regimens

- (a) There is no evidence to support the superiority of one regimen to the others.
 - (1) Lack of well-designed studies evaluating antibiotic regimens for NEC
 - (2) Most recent Cochrane review included only two trials from the 1980s that compared ampicillin plus gentamicin with the same regimen plus clindamycin or the same regimen plus enteral gentamicin.
- (b) Gram-positive coverage can be provided by ampicillin or vancomycin.
- (c) Gram-negative coverage can be provided by an aminoglycoside or a third-, or fourth-generation cephalosporin.
- (d) Anaerobic coverage (e.g., clindamycin, metronidazole) is added if there is evidence of bowel perforation or peritonitis (i.e., surgical NEC). Some institutions routinely add anaerobic coverage for all cases of NEC.
 - (1) Mortality benefit of adding anaerobic coverage in medical NEC has not been shown.
 - (2) Neonates randomized to receive ampicillin plus gentamicin and clindamycin had a statistically higher risk of strictures than those who received ampicillin plus gentamicin alone.
- (e) The specific antimicrobial agents used should be based on an individual unit's antibiogram.
- (f) Optimal duration is not known; in clinical practice, duration is generally based on Bell's staging.
 - (1) Bell's stage I: Often 48–72 hours, “rule out” NEC
 - (2) Bell's stage IIa: 7–10 days
 - (3) Bell's stages IIb and III: 10–14 days

D. Prevention

1. Because NEC can rapidly evolve from early signs of intestinal pathology to fulminant necrosis despite medical therapy, primary prevention should be the therapeutic goal.
2. Antenatal corticosteroids
 - a. Shown to augment intestinal maturation.
 - b. Conflicting results regarding effect on incidence of NEC; some studies show reduced incidence, whereas others show more NEC (may be owing to the improved survival of very preterm neonates because of decreased pulmonary morbidity).
3. Feeding protocols that emphasize the use of early trophic feedings (to promote peristalsis) and breast milk (contains maternal IgA) may help decrease NEC.
4. Probiotics: Augment intestinal maturation, reduce growth and colonization by potentially pathogenic organisms, increase amounts of anti-inflammatory cytokines
 - a. Consist mainly of strains of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces*.
 - b. Studies have shown at least a 30% reduction in NEC and a significantly reduced mortality.
 - c. A few case reports of sepsis caused by probiotic bacterial strains exist; however, larger reports of probiotic use have not shown an increased risk.
 - d. Probiotics are not yet considered standard of care because several unanswered questions remain: What is the optimal species or combination of species of probiotic? What is the optimal dosing and duration of therapy? When should probiotics be initiated and in whom? Should probiotics be U.S. Food and Drug Administration (FDA) regulated (currently classified as supplements)? Are these products safe, especially in light of reports of contamination with *Rhizopus*?

5. Oral antibiotics
 - a. Orally administered gentamicin has been shown to decrease the incidence of NEC.
 - b. Not routinely recommended because of a higher rate of colonization with resistant organisms in neonates receiving prophylactic oral antibiotics.

VII. PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN

A. Background

1. Characterized by elevated pulmonary pressures after birth in conjunction with a right-to-left shunt across the ductus arteriosus or foramen ovale.
 - a. Previously called persistent fetal circulation.
 - b. Imbalance of relative excess of endogenous vasoconstrictors (e.g., endothelin-1, thromboxane A₂) to endogenous vasodilators (e.g., nitric oxide, prostacyclin)
 - c. Usually transient; may be idiopathic or secondary to an underlying disease.
 - d. Affects primarily term neonates.
2. Causes of secondary pulmonary hypertension
 - a. Congenital diaphragmatic hernia
 - b. Meconium aspiration syndrome
 - c. Pneumonia/sepsis
 - d. RDS
 - e. BPD
 - f. Congenital heart defects
 - g. In utero drug exposure: Can occur after in utero exposure to nonsteroidal anti-inflammatory drugs or selective serotonin reuptake inhibitors.

B. Clinical Presentation

1. Symptoms: Evidence of respiratory distress, tachypnea, oxygen desaturation, cyanosis
2. Oxygenation index (OI): Used as an indication of disease severity.
 - a. $OI = (\text{mean airway pressure} \times FiO_2 \times 100) / PaO_2$
 - b. Relatively mild: OI of 15–25
 - c. Moderate: OI of 25–40
 - d. Severe: OI greater than 40
3. ECHO findings: Right-to-left shunt across the ductus arteriosus or foramen ovale, tricuspid valve regurgitation as a result of elevated pulmonary vascular pressure, and right ventricular hypertrophy.

Patient Case

7. A 3700-g boy was born at 38 weeks' gestational age by cesarean section for maternal preeclampsia. In the delivery room, he required positive pressure ventilation because of a lack of spontaneous respiratory effort. Apgar scores were 2, 5, and 7 at 1, 5, and 10 minutes, respectively. He was intubated and transferred to the NICU, where his initial blood gas shows a severe respiratory acidosis. His oxygen saturation is 87% on an FiO_2 of 100%. Despite efforts to optimize his oxygenation and mechanical ventilation, he remains cyanotic with an oxygenation index of 30. An urgent ECHO revealed no structural cardiac defects other than a PDA with a right-to-left shunt, tricuspid valve regurgitation, and an elevated right-sided pressure by Doppler flow. A diagnosis of persistent pulmonary hypertension of the newborn (PPHN) is made. Which drug is the best therapy to initiate in this patient?

- A. Bosentan
- B. Inhaled nitric oxide
- C. Milrinone
- D. Sildenafil

C. Treatment

1. Goals: Maintain systemic blood pressure to overcome right-to-left shunt and decrease pulmonary vascular resistance to facilitate oxygenation.
2. Supportive therapies
 - a. Inotropic and vasopressor agents: To support cardiac function and maintain systemic blood pressure
 - b. Sedatives/analgesics: Agitation and pain can worsen pulmonary vasoconstriction.
 - c. Neuromuscular blocking agents: Usually reserved for neonates who respond inadequately to appropriate sedation/analgesia.
 - d. Surfactant replacement
 - i. Shown to improve oxygenation and reduce the need for extracorporeal membrane oxygenation (ECMO) when PPHN is secondary to RDS, pneumonia/sepsis, or meconium aspiration (i.e., disease states in which surfactant deficiency/inactivation occurs).
 - ii. Greatest benefit in those with relatively mild disease
 - e. ECMO: May be indicated for severe pulmonary hypertension.
3. Targeted therapies: Overall lack of well-designed studies of the neonatal population; therefore, no validated treatment algorithm or clear roles for the various drug classes. See Cardiology chapter for discussion of treatment of pulmonary hypertension in older children.
 - a. Inhaled nitric oxide
 - i. Treatment of choice; provides selective vasodilation of the pulmonary circulation.
 - ii. Initiated at 20 ppm; gradual weaning of the dose before discontinuation is necessary to minimize the risk of rebound pulmonary hypertension.
 - (a) Sildenafil: A single dose, 0.4 mg/kg, of enteral sildenafil given when inhaled nitric oxide has been weaned to 2 ppm was shown to prevent rebound pulmonary hypertension on inhaled nitric oxide discontinuation.
 - (b) The use of agents other than sildenafil to facilitate weaning of inhaled nitric oxide has not been studied.

- b. Prostacyclin analogs: Prostacyclin produces vasodilation by stimulating cyclic adenosine monophosphate (cAMP) production.
 - i. Epoprostenol: Not a selective pulmonary vasodilator
 - (a) Administered by continuous intravenous infusion or inhalation; risk of rebound pulmonary hypertension owing to the drug's extremely short half-life if infusion or inhalation is interrupted
 - (b) Optimal dose is unclear; limited evidence suggests that neonates need higher doses than do adults with pulmonary hypertension.
 - (c) Systemic hypotension is the primary adverse effect.
 - ii. Iloprost
 - (a) Administration by nebulization through the ventilator circuit results in selective pulmonary vasodilation.
 - (1) Actuated inhalation delivery device is recommended by the manufacturer, but not compatible with ventilator circuits.
 - (2) Continuous-flow conventional nebulizers used in a ventilator circuit will result in significant drug loss.
 - (b) Optimal dose and frequency unclear; has a relatively short half-life.
- c. Phosphodiesterase (PDE) inhibitors
 - i. Sildenafil
 - (a) PDE-5 inhibition increases cyclic guanosine monophosphate, a second messenger in the nitric oxide pathway, resulting in pulmonary vasodilation.
 - (b) Case reports and small studies used a wide range of enteral doses; showed short-term beneficial effect, but long-term safety and efficacy are unknown.
 - (c) Small case series reported on the improvement in short-term respiratory parameters with the use of intermittent intravenous sildenafil. Optimal dosing regimen for this route is unknown.
 - (d) Systemic hypotension, although rare, has been reported.
 - (e) Concerns for increased mortality in older children (1–17 years) with pulmonary hypertension led the FDA to caution against the use of sildenafil in children.
 - (1) STARTS-1 and STARTS-2 trials did not include neonates.
 - (2) Sildenafil was used as monotherapy, regardless of disease severity, in these studies.
 - (3) The mortality rate of 16% in the high-dose group (more than 3 mg/kg/day) is lower than the historical rates of 33%–52% before the availability of targeted therapies.
 - ii. Milrinone
 - (a) PDE-3 inhibition increases cAMP, leading to pulmonary vasodilation.
 - (b) May be useful in combination with inhaled nitric oxide, which has been shown to increase PDE-3 activity.
 - (c) The optimal dose and role in the treatment of PPHN are not known.
- d. Endothelin receptor antagonists
 - i. Bosentan
 - (a) Dual endothelin receptor antagonist that blocks the vasoconstricting effect of endothelin
 - (b) Optimal dosing not known; available only as enteral extemporaneous formulation.
 - (c) Short-term benefit of improved oxygenation shown in small case reports/trials, but no studies of long-term safety or efficacy.
 - (d) Adjunctive therapy for PPHN did not shorten time to wean from inhaled nitric oxide or mechanical ventilation in a small, randomized trial, possibly due to impaired enteral absorption or severity of illness in bosentan group.
 - (e) Black box warning for hepatotoxicity in the adult labeling

- ii. Ambrisentan
 - (a) Selective endothelin-A receptor antagonist blocks vasoconstricting effect of endothelin-1 and promotes clearance of endothelin-1.
 - (b) No black box warning for hepatotoxicity.
 - (c) No data regarding use or pharmacokinetics in neonates. Known to have a longer half-life in adults than bosentan; may be expected to be even longer in neonates, which would not be ideal because it increases the potential risk of prolonged systemic hypotension and other adverse effects.
- 4. The treatment duration is relatively short (3–10 days) for PPHN, although neonates with underlying structural changes (e.g., BPD) may require prolonged therapy.

VIII. CONGENITALLY ACQUIRED INFECTIONS

A. Herpes Simplex Virus (HSV)

- 1. Background
 - a. HSV type 2 is the most common cause of neonatal herpes disease.
 - b. Transmission is usually during vaginal birth by an infected maternal genital tract; may also be an ascending infection through the amniotic membranes (ruptured or intact).
 - i. If a pregnant woman has active genital lesions, a cesarean delivery can reduce the risk of transmission to the neonate.
 - ii. Suppressive therapy with oral acyclovir or valacyclovir given near the end of pregnancy to a woman with a history of HSV infection can reduce, but not eliminate, the risk of transmission.
 - c. Risk of transmission to the neonate
 - i. Highest (60%) in those born to mothers with first-episode primary genital infection, followed by those born to mothers with first-episode nonprimary infection (25%).
 - ii. Transmission from a mother with recurrent HSV infection is low (less than 2%).
- 2. Presentation
 - a. Disseminated disease: Involves several organ systems, especially the lungs and liver; may involve the CNS.
 - i. Around 25% of neonatal HSV cases
 - ii. Around 60% will have skin lesions.
 - iii. Typically presents within 1–2 weeks after birth. Should be suspected in a septic-appearing neonate with negative bacteriologic cultures and severe liver dysfunction.
 - b. Localized CNS disease
 - i. 30% of neonatal HSV cases
 - ii. Around 66% will have skin lesions.
 - iii. Presentation may be later, between 2 and 3 weeks after birth. Suspect especially if onset of seizures is 2 weeks or more after birth.
 - c. Localized skin, eyes, and mouth (SEM) disease
 - i. 45% of neonatal HSV cases
 - ii. Most (more than 80%) will have skin vesicles.
 - iii. Typically presents within 1–2 weeks after birth.
 - d. Associated with high morbidity and mortality rates, despite appropriate antiviral treatment.
- 3. Diagnosis
 - a. Definitive diagnosis: Isolation of HSV by culture
 - i. Scraping of skin vesicles for culture
 - ii. “Surface cultures”: Swabs of the conjunctivae, mouth, nasopharynx, and rectum performed at about 24 hours after birth

- b. PCR testing of CSF is used for confirming CNS involvement.
 - i. Persistently positive PCR assay of the CSF after treatment is associated with poor outcomes.
 - ii. A repeat specimen should be tested near the end of the treatment course to confirm the clearance of HSV from the CSF; therapy should continue until the result is negative.
- c. PCR testing of blood: Usefulness for guiding the length of therapy is unknown.

Patient Case

8. A 3400-g girl is born by cesarean section at 37 weeks' gestational age to a mother with a history of genital HSV infection and visible genital lesions at delivery. The neonate appears well and begins feeding within a few hours after birth. Surface cultures for HSV are sent at 24 hours of age and are subsequently reported as positive. Intravenous acyclovir is initiated. Cerebrospinal fluid for HSV PCR and serum ALT are sent. The neonate remains asymptomatic. The HSV PCR is negative, and the ALT is 120 units/L (range 5–45 units/L). Which is the best recommendation regarding this patient's treatment?
- A. Discontinue acyclovir.
 - B. Continue acyclovir 60 mg/kg/day intravenously in three divided doses to complete 14 days of treatment.
 - C. Continue acyclovir 60 mg/kg/day intravenously in three divided doses to complete 21 days of treatment.
 - D. Switch to oral acyclovir 300 mg/m²/dose every 8 hours to complete 10 days of treatment.

4. Treatment

- a. Management of neonates with symptomatic/proven HSV disease
 - i. Intravenous acyclovir
 - (a) Dose: 20 mg/kg/dose every 8 hours; recommended to prolong interval to every 12 hours in premature neonates.
 - (b) Duration
 - (1) SEM disease: 14 days
 - (2) Disseminated or localized CNS disease: Minimum of 21 days
 - (c) Monitoring: Twice-weekly neutrophil count is recommended.
 - (d) Add topical ophthalmic drug (e.g., trifluridine or ganciclovir) with ocular involvement.
 - ii. Oral acyclovir
 - (a) Not recommended for treatment of HSV infections.
 - (b) Used as suppressive therapy after treatment of an acute HSV infection.
 - (1) Shown to prevent skin recurrences: Occurs in 50% of infants after neonatal HSV infection.
 - (2) Improves neurodevelopmental outcomes after CNS disease.
 - (3) Regimen: 300 mg/m²/dose given three times daily for 6 months.
 - (4) Valacyclovir not studied and therefore should not be used for this indication.

- b. Management of **asymptomatic** neonates born to women with active genital HSV lesions (Figures 1 and 2)

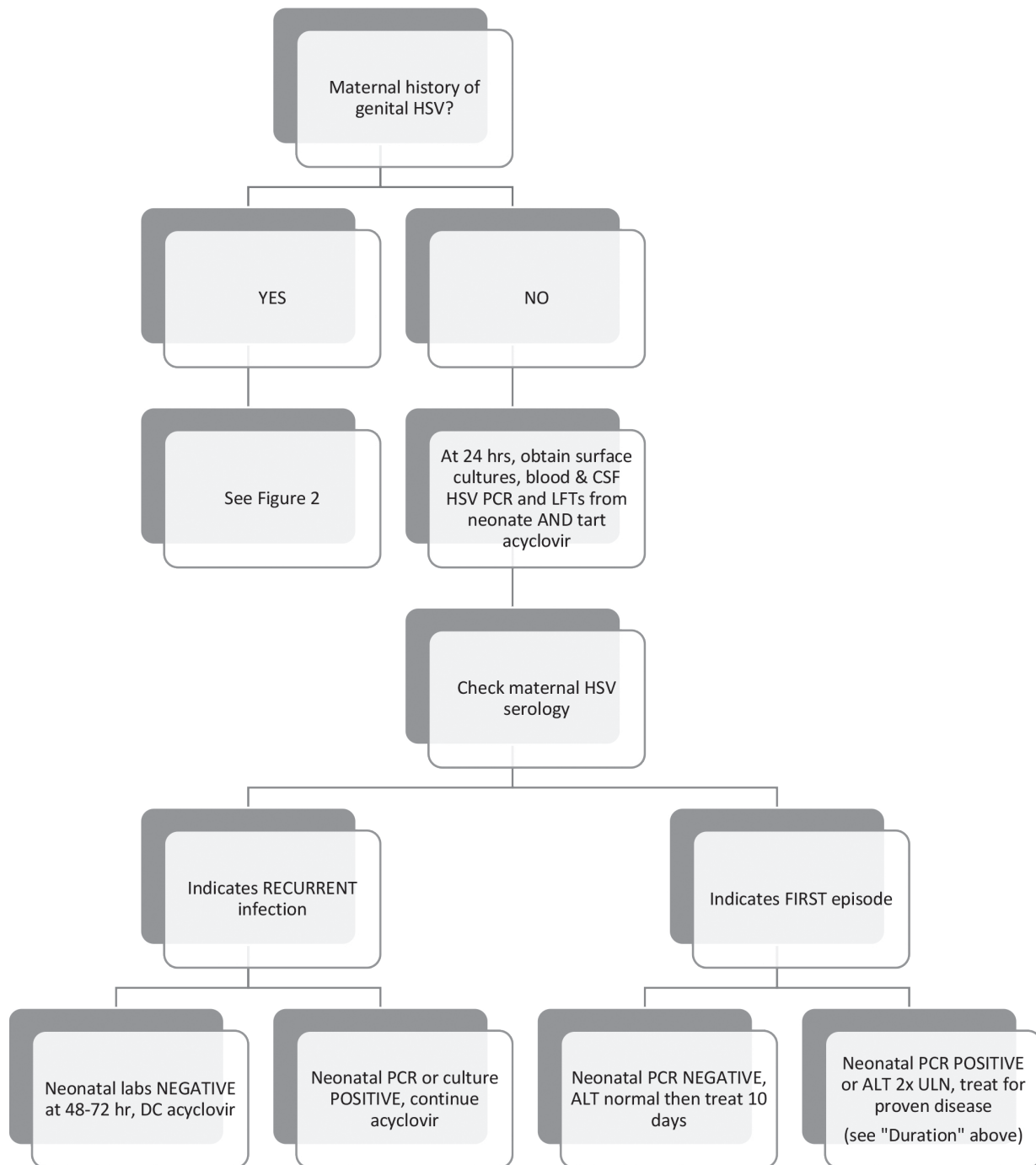


Figure 1. Management of asymptomatic neonates born to women with active genital herpes simplex virus (HSV) lesions and no history of genital HSV.

ALT = alanine aminotransferase; CSF = cerebrospinal fluid; DC = discontinue; LFT = liver function test; PCR = polymerase chain reaction; ULN = upper limit of normal.

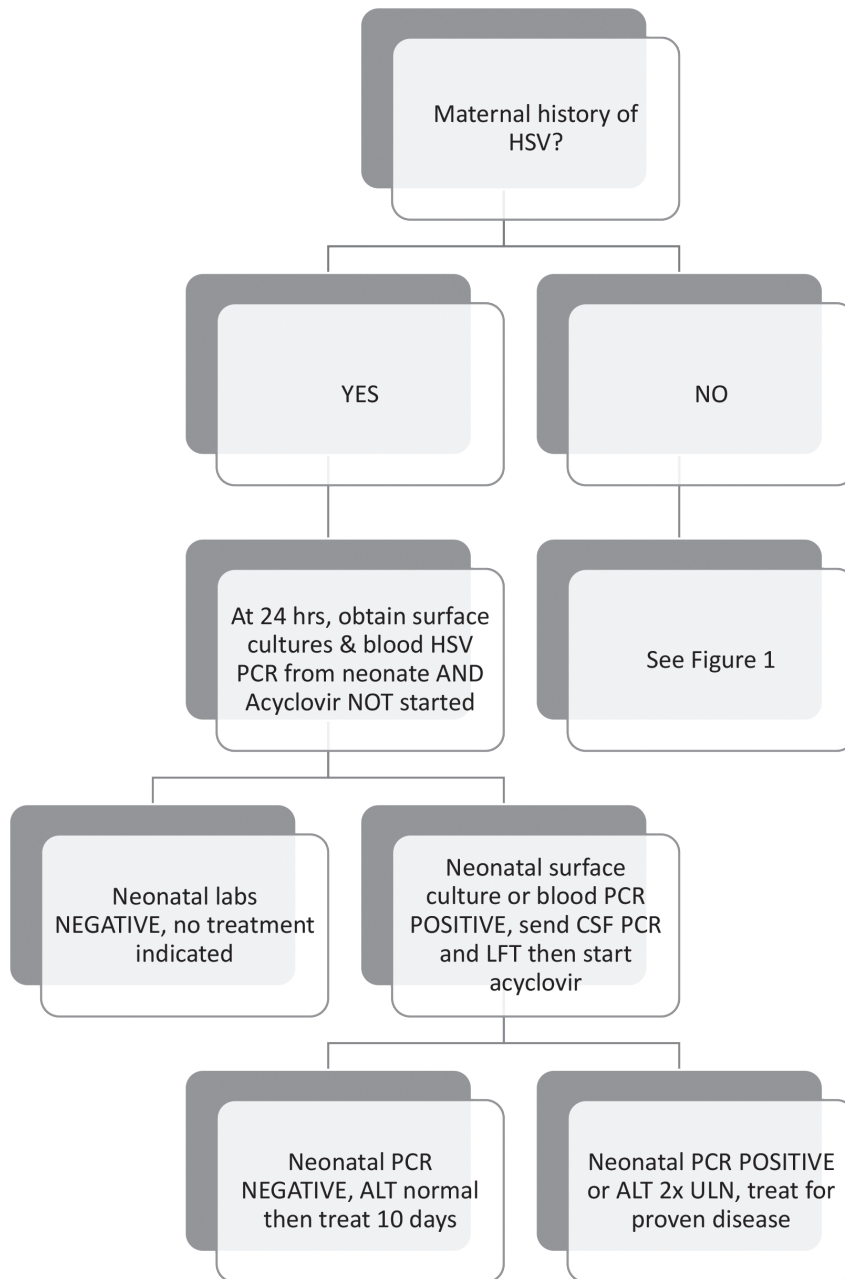


Figure 2. Management of asymptomatic neonates born to women with active genital herpes simplex virus (HSV) lesions and a history of genital HSV.

ALT = alanine aminotransferase; CSF = cerebrospinal fluid; LFT = liver function test; PCR = polymerase chain reaction; ULN = upper limit of normal.

B. Congenital Syphilis**1. Background**

- a. Transmission of *Treponema pallidum* usually occurs transplacentally; also can occur as a result of contact with active lesion during birth.
 - i. Transmission rates are 60%–100% in primary and secondary syphilis.
 - ii. Rates in early latent (40%) and late latent (8%) infections are lower.
- b. Spontaneous abortion or stillbirth is common if maternal infection is untreated.

2. Presentation

- a. Two-thirds of neonates will be asymptomatic at birth.
- b. Early signs include hepatosplenomegaly, rash, neurosyphilis, rhinitis (“snuffles”), leukocytosis, hemolytic anemia, thrombocytopenia, bony involvement, and skin lesions.
- c. Late manifestations include “saddle-nose deformity” (from snuffles related to nasal cartilage destruction), frontal bossing, bowing of mid-tibia, synovial effusions, tooth abnormalities (“Hutchinson teeth,” “mulberry molars”), and perforated hard palate.
 - i. Usually occur after 2 years of age.
 - ii. Can be prevented if the neonate receives treatment for early infection.

Patient Case

9. A 3900-g boy was born at 38 weeks’ gestational age to a mother with a history of syphilis that was adequately treated 6 weeks before delivery. The mother has shown no signs of relapse or recurrence since treatment. Maternal syphilis rapid plasma reagin (RPR) is 1:16. In the delivery room, the neonate had some grunting and retractions. He was transferred to the NICU and initiated on ampicillin 100 mg/kg/dose intravenously every 8 hours and gentamicin 5 mg/kg/dose intravenously every 24 hours to rule out sepsis/pneumonia. Syphilis RPR was sent for the neonate, and the result was 1:16. The neonate’s symptoms resolved within 6 hours after birth, and blood cultures remained negative at 48 hours. Which is the best recommendation regarding this patient’s treatment?
- A. Continue ampicillin and gentamicin. No treatment is indicated for congenital syphilis.
 - B. Discontinue gentamicin and continue ampicillin to complete 10 days for congenital syphilis.
 - C. Discontinue ampicillin and gentamicin. Give benzathine penicillin G 50,000 units/kg intramuscularly x 1 dose for congenital syphilis.
 - D. Discontinue ampicillin and gentamicin. Give aqueous penicillin G 50,000 units/kg/dose intravenously every 12 hours for 10 days for congenital syphilis.

3. Treatment

- If the maternal RPR (test)/Venereal Disease Research Laboratory [test for syphilis] (VDRL) is reactive but the maternal treponemal test is nonreactive, no treatment for the neonate is required.
- If the maternal RPR/VDRL and treponemal tests are reactive, determining the need to treat the neonate depends on the maternal treatment (Figure 3).

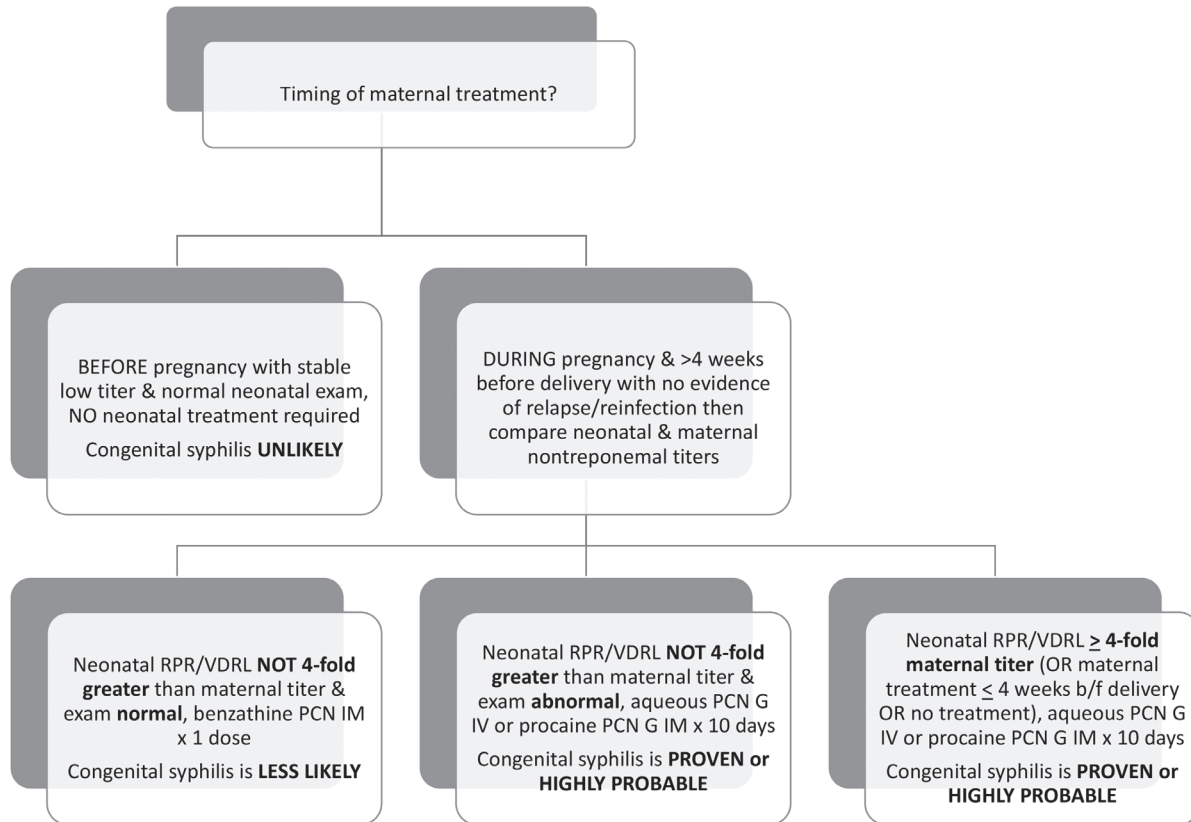


Figure 3. Treatment of congenital syphilis.

b/f = before; IM = intramuscularly; IV = intravenously; PCN = penicillin; RPR = rapid plasma reagin; VDRL = Venereal Disease Research Laboratory.

- 10 full days of penicillin is preferred, even if the neonate originally received ampicillin for possible sepsis.
- The entire course must be repeated if more than 1 day of therapy is missed.

C. Toxoplasmosis

1. Presentation

- Death often results if transmission occurs in the first trimester.
- "Classic triad" of hydrocephalus, intracranial calcifications, and chorioretinitis may occur if transmission occurs during the second trimester.
- Other complications include hepatosplenomegaly, developmental delay, hearing loss, and seizures.

2. Treatment

- Pyrimethamine plus sulfadiazine plus leucovorin (folinic acid) for 1 year
- Optimal dosing regimen is not known.

D. Cytomegalovirus (CMV)**1. Presentation**

- a. Most neonates with congenital CMV will be asymptomatic at birth.
- b. Manifestations include intrauterine growth restriction (i.e. birth weight below the 10th percentile), microcephaly, periventricular calcifications, jaundice, hepatosplenomegaly, retinitis, “blueberry muffin” rash, petechiae
 - i. Mildly symptomatic: One or two isolated findings that are transient.
 - ii. Moderately to severely symptomatic: Multiple findings consistent with congenital CMV or any CNS involvement.
- c. Long-term complications include developmental delay and deafness.

2. Treatment

- a. Typically, antiviral therapy is reserved for neonates with moderate to severe symptoms caused by CMV disease. Mildly symptomatic and asymptomatic infants, including those with isolated sensorineural hearing loss, should not be treated with antivirals.
- b. Oral valganciclovir 16 mg/kg/dose twice daily for 6 months
 - i. May be of benefit in reducing the risk of hearing loss and decreasing the severity of developmental impairment.
 - ii. Ganciclovir 6 mg/kg/dose intravenously every 12 hours is an alternative.
 - iii. Should be initiated within 1 month after birth.
 - iv. Monitoring: Transaminases (monthly during treatment) and absolute neutrophil count (weekly for 6 weeks then at week 8 then monthly until completion of treatment)

E. Hepatitis B Virus**1. Presentation**

- a. Most neonates with perinatally acquired hepatitis B virus are asymptomatic; some may have signs of hepatitis.
- b. Long-term complications include hepatocellular carcinoma and cirrhosis.

2. Treatment

- a. There is no treatment for acute hepatitis B infection.
- b. The risk of developing hepatitis B infection can be reduced by postexposure prophylaxis.
 - i. If the mother is positive for HBsAg, the neonate should receive hepatitis B vaccine and HBIG within 12 hours of birth.
 - ii. If the mother’s HBsAg status is unknown at delivery, she should be tested immediately AND the neonate should receive the hepatitis B vaccine within 12 hours of birth. If the mother’s HBsAg is positive, HBIG should be administered to the neonate within 7 days of birth.
 - (a) Preterm neonates with a birth weight less than 2 kg born to mothers whose HBsAg status is unknown should receive the hepatitis B vaccine within 12 hours of birth. If the mother’s HBsAg status remains unknown at 12 hours after birth, the neonate should also receive HBIG within 12 hours of birth.
 - (b) In this circumstance, the hepatitis B vaccine given to the preterm neonate should not be counted toward completion of the routine vaccine series.

IX. NEONATAL ABSTINENCE SYNDROME**A. Screening for Intrauterine Drug Exposure**

1. Maternal characteristics (e.g., history of drug use, late or no prenatal care, many spontaneous abortions, severe mood swings, abruptio placentae) consistent with drug abuse may prompt screening of the neonate.

2. Methods for screening: Natural opioids are readily detectable in urine or meconium; semisynthetic and synthetic opioids as well as “designer drugs” are not detected by routinely used laboratory tests.
 - a. Urine
 - i. Must be performed soon after birth.
 - (a) Beware of false positives owing to maternal drug administration during the peripartum period.
 - (b) False negatives may occur because of maternal drug abstinence shortly before delivery.
 - ii. May detect only recent drug exposure because of the rapid clearance of many drugs.
 - (a) Opioids, cocaine metabolites, amphetamines, and short-acting benzodiazepines are typically cleared within 1–3 days.
 - (b) Long-acting barbiturates and benzodiazepines may be detectable for a longer period.
 - b. Meconium: Earliest stool; contains ingested material from swallowing amniotic fluid; typically thick, sticky, and very dark green.
 - i. Many drugs concentrate in meconium, especially those excreted through the fetal hepatobiliary system or into amniotic fluid by renal elimination.
 - ii. The window of detection (from 20 weeks’ gestation) is much longer than for urine testing.
 - iii. Sample must be meconium; cannot include transitional or breast milk/formula-fed stools (typically thinner and yellow).
 - iv. Results may be delayed because the sample often is not processed within the hospital laboratory and must be sent to a reference laboratory.
 - v. A positive result is not predictive of neonatal abstinence syndrome (NAS).
 - c. Other biological samples such as umbilical cord blood and neonatal hair have also been used for screening.

Patient Case

10. A 2600-g girl was born at 36 weeks’ gestational age to a mother in a methadone treatment program for heroin addiction. The mother has received methadone 80 mg daily for the past 7 months and has been adherent. The neonate is admitted to the NICU for initial respiratory distress in the delivery room and for monitoring of withdrawal symptoms. Finnegan scores have been assessed every 4 hours since birth, and the nurse indicates that she has been crying “a lot” and is very “irritable.” Scores for the first 24 hours are 4, 6, 5, 8, 7, and 8. Which is the best recommendation for the treatment of this neonate at risk of abstinence syndrome?
 - A. No pharmacologic intervention for withdrawal is currently indicated.
 - B. Start clonidine.
 - C. Start methadone.
 - D. Start phenobarbital.

B. Clinical Presentation

1. Onset of symptoms depends on drug to which fetus was exposed and timing of drug use before delivery; neonatal opioid withdrawal syndrome (NOWS) is most common.
 - a. Heroin: Within 24 hours after birth
 - b. Methadone: Within 2–6 days after birth
 - c. Buprenorphine: Within 2–3 days after birth
 - d. 55%–94% of neonates exposed to opioids in utero will have withdrawal.
 - e. Non-opioid substances (e.g., alcohol, barbiturates, cocaine, caffeine, selective serotonin reuptake inhibitors) may cause symptoms consistent with withdrawal; however, the routine need for pharmacologic treatment of these neonates has not been established.

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2. Symptoms manifest in the autonomic (e.g., sweating, fever, yawning, sneezing), neurologic (e.g., tremors; high-pitched, continuous crying; increased muscle tone; seizures), and GI systems (e.g., loose stools, vomiting, poor feeding).
 3. Scoring tools
 - a. Modified Finnegan score: Most commonly used assessment tool
 - i. Neonate is evaluated every 3–4 hours, after feeding. Score should include signs and symptoms present at the time of the evaluation as well as at any time since the previous evaluation.
 - ii. If three consecutive scores are 8 or higher or if two consecutive scores are 12 or higher, pharmacologic therapy should be initiated.
 - iii. After symptoms are controlled, scores are often used in clinical practice to gradually wean therapy.
 - b. Maternal Opioid Treatment: Human Experimental Research (MOTHER) modification
 - i. Used for initiation, advancement, and weaning of therapy for neonatal opioid withdrawal syndrome
 - ii. If consistent score of 9–12 or a single score of 13 or higher, pharmacologic therapy should be initiated.
 - c. Eat, Sleep, Console (ESC)
 - i. Assesses infant's ability to eat 1 or more oz or breastfeed well, sleep 1 hour or more, and be consoled.
 - ii. Emphasizes environmental effects and nonpharmacologic approaches before initiating or escalating drug therapy.
 4. Risk factors
 - a. Gestational age
 - i. Symptoms tend to be milder in premature neonates.
 - ii. May be related to immaturity of CNS, lower fat deposits of drug, and decreased total time for drug exposure.
 - b. Drug to which fetus was exposed
 - i. Polysubstance exposure is associated with increased severity of NAS.
 - ii. Variable reports related to the incidence and severity of NAS based on the drug to which the neonate was exposed in utero (e.g., there are reports of higher incidence/severity of NAS after methadone exposure compared with buprenorphine or heroin, whereas others report no difference among the drugs)
 - iii. Higher maternal methadone dose has not been shown to correlate with a greater incidence or severity of NAS.
- C. Treatment
1. Nonpharmacologic
 - a. Swaddling; minimal handling; reduced environmental noise; subdued lighting; frequent, small feedings
 - b. Nonpharmacologic interventions should be used in all cases and may suffice for cases of mild withdrawal.
 2. Pharmacologic: Indicated for moderate to severe symptoms; only known benefit is short-term relief of signs and symptoms; NAS is self-limited.
 - a. Opioids
 - i. Morphine versus methadone
 - (a) Morphine is the most commonly used agent.
 - (b) Methadone has a significantly longer and more variable half-life (4–62 hours).
 - (c) The shorter half-life of morphine necessitates more frequent dosing but allows for easier dose titration.
 - (d) Both are available as alcohol-free products.
-

- (e) There is no difference in treatment outcomes or length of stay when comparing methadone-treated neonates with those treated with morphine.
 - (f) Although many institutions have protocols for dose titration, no specific dose or regimen has been proven superior.
 - ii. Tincture of opium
 - (a) Contains 25-fold higher concentration of morphine than does oral morphine solution.
 - (1) Increased risk of medication error when dosing or diluting the product
 - (2) Increased risk of morphine overdose
 - (b) Contains alcohol; no longer used commonly
 - iii. Buprenorphine
 - (a) Partial μ -opioid receptor agonist with a long, but predictable half-life (72 hours)
 - (b) Administration to neonates requires compounding a sublingual solution that contains alcohol. Significant first-pass metabolism necessitates sublingual administration.
 - (c) Limited evidence suggests a decreased length of treatment and hospital stay compared with morphine; however, safety and efficacy need further investigation in larger studies.
- b. Clonidine
 - i. Central α_2 -adrenergic receptor agonist
 - ii. Thought to reduce symptoms of autonomic overactivity by decreasing central catecholamine release.
 - iii. When used in combination with morphine, shown to reduce total morphine dose and shorten treatment duration and length of stay.
 - iv. No significant hypotension or bradycardia reported.
 - v. Requires extemporaneous preparation of an oral solution.
- c. Phenobarbital
 - i. Prolonged half-life (67–115 hours)
 - ii. May be most beneficial as an adjunctive therapy in polysubstance exposure or non-opioid withdrawal.
 - iii. Not as effective as an opiate agent for monotherapy of opioid withdrawal; does not improve GI symptoms or prevent seizures.
 - iv. Concerns about detrimental neurodevelopmental effects exist.
- d. Agents that are not recommended for treatment of NAS:
 - i. Naloxone: Maternal opioid use is a relative contraindication to naloxone administration to the neonate for apnea/hypoventilation after birth; may precipitate acute withdrawal and seizures.
 - ii. Paregoric: Used commonly historically, but no longer recommended because it contains several opioids as well as toxic ingredients, including camphor, anise oil, alcohol, and benzoic acid.
 - iii. Benzodiazepines: Not shown to be effective for treating opioid withdrawal symptoms.

X. DRUGS IN PREGNANCY AND LACTATION

A. Teratogenesis

1. Clinical perspective: The risk of major malformations in the general population, with or without drug therapy, is about 2%–3%.
2. Teratogenicity results from in utero exposure to a drug(s) or substance associated with irreversible structural abnormalities or functional damage.
 - a. Can cause embryopathy or fetopathy.
 - b. Highest risk of structural abnormalities occurs from 5 to 10 weeks' gestation; organogenesis occurs during this "embryonic" period.

- c. Fetotoxicity can occur any time between the late first trimester and birth.
 - d. Teratogenicity can also occur when the male partner, rather than the mother, is taking the offending drug.
3. Common teratogenic effects: Neural tube defects, congenital heart defects, cleft lip/palate, stillbirth

Patient Case

11. A 32-year-old woman is seen by her physician for symptoms of depression. She is 30 weeks pregnant and has not previously taken medication for her depression. She has chronic hypertension that is well controlled but no other significant medical history. Her current medications include a prenatal vitamin and methyldopa. The physician is considering three different drugs with which to treat her depression. Drug 1 is pregnancy category B. Drugs 2 and 3 are pregnancy category C. Which is the best assessment of the risk of these drugs when used in a pregnant woman?
- A. Drugs 2 and 3 have a higher risk of fetal harm than drug 1.
 - B. Drugs 2 and 3 have the same level of risk (i.e., are equally as safe in pregnancy).
 - C. Drugs 1, 2, and 3 may all be acceptable options for treating this mother's depression.
 - D. This mother's depression should not be treated during pregnancy because the risks outweigh the benefit.

B. Risk Categories

- 1. "Old" FDA pregnancy risk categorization

Table 5. FDA Pregnancy Risk Categories

Pregnancy Category	Explanation
A	Controlled studies of pregnant women have not shown an increased risk of fetal abnormalities
B	Animal studies show no evidence of fetal harm; however, there are no adequate studies of pregnant women -OR- Animal studies show adverse effects; however, adequate studies of pregnant women did not show fetal harm
C	Animal studies show adverse effects on the fetus, but there are no adequate studies of pregnant women -OR- There are no animal studies or adequate studies of pregnant women
D	Studies of pregnant women have shown fetal harm, but the potential benefits of therapy may outweigh the potential risk
X	Studies of pregnant women have shown that fetal harm and the risk to the fetus clearly outweigh the potential benefit of the therapy. The drug is contraindicated in pregnant women

- a. Misconceptions
 - i. The risk of severe fetal harm increases from category A to X: The categories are not a scale of harm; rather, they show the degree of evidence for fetal harm.
 - ii. The "risk" is only that of fetal harm: The potential harm to the mother from withholding the therapy must also be considered.
 - iii. All drugs within the same category have the same level of risk (e.g., oral contraceptives are primarily classified as category X because there is no benefit to trying to prevent pregnancy in a woman who is already pregnant. In contrast, warfarin is classified as category X for most indications because it is associated with known embryopathy).

- b. This classification system does not account for timing of exposure, severity of fetal harm, or potential treatability of the fetal injury.
- 2. Lactation risk categories
 - a. Weighing the risk-benefit of using a medication during lactation includes several factors:
 - i. Necessity of the drug for the mother
 - ii. Potential effect on milk production
 - iii. Concentration of the drug in breast milk
 - iv. Potential for oral absorption in the breastfed infant
 - v. Possible adverse effects from the drug in the breastfed infant
 - vi. Age of the infant: Infants younger than 2 months are reported to have the highest incidence of adverse effects from drug exposure during breastfeeding; reports are rare in infants older than 6 months.
 - vii. Benefits of breastfeeding to the infant and mother
 - b. Other factors that may affect the decision to use a drug in a lactating woman include:
 - i. Is the drug being continued after in utero exposure or is it a newly initiated therapy?
 - ii. Is the therapy a single-dose or short course as opposed to chronic therapy?
 - iii. Are the risks associated with a potential adverse event higher in a preterm infant or one with underlying illness compared with a term or otherwise healthy infant?
 - c. No formal classification system; most often cited as recommended/not recommended or compatible/not compatible with breastfeeding.
 - d. Dr. Thomas Hale's lactation risk categories
 - i. L1 Compatible: Controlled trials of breastfeeding women did not find infant harm, or the product is not orally bioavailable.
 - ii. L2 Probably Compatible: Limited trials of breastfeeding women did not find infant harm, or if harm was shown, the likelihood was low.
 - iii. L3 Probably Compatible: No controlled trials of breastfeeding women, but a risk of adverse effects in the infant is possible; or controlled trials show only minimal, non-life-threatening adverse effects. Drug should be taken by a breastfeeding woman only if the potential benefits outweigh the potential risks to the infant.
 - iv. L4 Possibly Hazardous: Evidence of adverse effects to the infant exist, but the benefit to the breastfeeding mother may justify the risk to the infant.
 - v. L5 Hazardous: Trials of breastfeeding women have shown a significant harm to the infant or the drug is associated with a high risk of harm to the infant. Drug is contraindicated in breastfeeding women.
- 3. New FDA Pregnancy and Lactation Labeling Rule
 - a. Labeling for pregnancy and lactation are similar and include:
 - i. Risk summary: Describes the likelihood that the drug will increase the risk of fetal/infant harm according to available data.
 - ii. Clinical considerations: Describes the risk to the fetus after inadvertent exposure; risk to the pregnant woman and fetus from the disease for which the drug is prescribed; effects related to dose, timing, and duration of exposure; potential neonatal complications and potential monitoring/management options; potential effect on milk production; and techniques to minimize infant drug exposure (in Lactation section).
 - iii. Data: Human and animal data are presented separately.
 - b. Also emphasizes the importance of patient enrollment in a registry, if one exists, to collect data about the effects of the medication when used during pregnancy and lactation.
 - c. All drugs submitted to the FDA after June 30, 2015, will use the new format; new labeling for drugs approved earlier will be phased in gradually.

Patient Case

12. A 2-month-old boy who was born at term and has no significant medical history is being breastfed. His mother is prescribed tobramycin ophthalmic solution 2 drops in both eyes every 4 hours for 10 days for a severe conjunctivitis. Which is the best recommendation regarding breastfeeding during this mother's treatment?
- Therapy should be switched to an agent with a higher molecular weight.
 - Tobramycin ophthalmic can be used, but breast milk should be discarded during therapy (i.e., "pump and dump") and formula used.
 - Tobramycin ophthalmic can be used, and breastfeeding can continue without modifications.
 - Tobramycin ophthalmic can be used, breastfeeding can continue, and the infant should receive probiotics.

C. Factors Affecting Drug Transport**1. Across the placenta**

- Molecular weight:** Substances with a mass below 500 Da readily diffuse across the placental barrier.
- Charge:** Nonionized substances are transported rapidly across the placenta by simple diffusion.
- Lipophilicity:** Highly lipid-soluble substances are transported rapidly across the placenta by simple diffusion.
- Protein binding:** Highly protein-bound substances are less likely to cross the placental barrier.

2. Into breast milk

- Maternal plasma concentration:** Most drugs enter by passive diffusion, so the higher the maternal plasma concentration, the more likely the drug will enter the breast milk.
- Molecular weight:** Low molecular weight increases the likelihood of drug excretion into milk.
- Charge:** Lack of ionization increases drug excretion into milk.
- Lipophilicity:** Highly lipid-soluble substances are more likely to be excreted into milk.
- Protein binding:** Highly protein-bound substances are less likely to be excreted into milk.
- Volume of distribution:** Drugs with a small volume of distribution are more likely to be excreted into milk.
- Half-life:** Drugs with long half-lives are likely to accumulate in milk.

D. Examples of Drugs Known to Be Teratogens

- Warfarin:** Skeletal defects if exposed in the first trimester; CNS defects, mental retardation, and micro-hemorrhages if exposed in second or third trimester.
- Valproic acid:** Neural tube defects; craniofacial, limb, cardiac and CNS abnormalities
- Phenytoin:** Fetal hydantoin syndrome can include craniofacial abnormalities, hypoplasia of the nails, cleft lip/palate, microcephaly, developmental delay.
- Methotrexate:** Embryopathy with many malformations
- Nonsteroidal anti-inflammatory drugs:** Cardiac malformations and gastroschisis if exposed during the first trimester; premature closure of the ductus arteriosus in a fetus if exposed during the third trimester.
- Angiotensin-converting enzyme inhibitors/angiotension II receptor blockers:** Cardiac malformations if exposed during the first trimester; renal failure if exposed in the second or third trimester.
- Tetracycline:** Staining of teeth if exposed in second or third trimester.

E. Examples of Drugs That Are Contraindicated in Lactation

- Antineoplastic agents
- Retinoids
- Tetracyclines: Chronic use
- Chloramphenicol
- Amiodarone

F. Strategies for Minimizing Exposure**1. Pregnancy**

- a. Counseling regarding teratogenic potential in any woman (or man) of childbearing potential
 - i. About 50% of pregnancies in the United States are unintended.
 - ii. Some medications require routine pregnancy testing before prescribing (e.g., bosentan).
- b. Planning for alternative, “safer” therapies before pregnancy occurs

2. Lactation

- a. “Pump and dump” is rarely the best solution.
- b. Try to breastfeed when maternal plasma concentrations are likely to be low: Difficult to do when the infant feeds every 3–4 hours.
- c. When possible, choose a drug with a short half-life.
- d. When possible, choose a drug that is highly protein bound.
- e. Consider relative infant dose (RID)
 - i. $\text{RID (\%)} = \frac{\text{infant's dose (mg/kg/day)}}{\text{mother's dose (mg/kg/day)}} \times 100$
 - ii. $\text{Infant's dose} = \text{average drug concentration in milk (mg/mL)} \times \text{estimated milk intake (mL/kg/day)}$
 - iii. RID less than 10% is considered relatively safe for use in breastfeeding, but infant and drug factors should be considered.
 - iv. RID is reported for many medications in references such as Hale’s Medications and Mothers’ Milk.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

This patient is at high risk of RDS because of extreme prematurity, lack of antenatal steroids, and male sex, so surfactant replacement therapy is indicated. Respiratory distress syndrome is usually diagnosed by clinical signs and symptoms. Although radiographic findings may be consistent with RDS, they are not required to make a diagnosis (Answer A is incorrect). Because this patient is at high risk of RDS, prophylactic surfactant administration is a reasonable consideration; however, the time interval for administration (at 10–30 minutes of life, ideally before positive pressure ventilation) has been missed, and the patient already has signs of RDS (Answer B is incorrect). Prophylactic therapy for all high-risk neonates results in overtreatment because not all of these neonates will progress to RDS. Early surfactant rescue therapy has been shown to reduce chronic lung disease and mortality compared with delayed rescue therapy (Answer D is incorrect). Because this patient has risk factors for RDS, has signs consistent with RDS, and early rescue therapy has benefits over delaying surfactant administration, early surfactant rescue therapy (within 2 hours of birth) should be administered (Answer C is correct).

2. Answer: B

Very few interventions, other than preventing preterm birth, have been shown efficacious in preventing BPD. Several pharmacologic interventions theoretically should prevent BPD, but clinical trials have not confirmed this benefit. Macrolide antibiotics (e.g., azithromycin) have been studied for the prevention of BPD because colonization with *Ureaplasma* in the neonate has been associated with the development of BPD. However, clinical trials did not show a reduced incidence of BPD when all high-risk neonates were given macrolide prophylaxis (Answer A is incorrect). A subset of neonates with a positive PCR result for *Ureaplasma* who were treated with azithromycin were shown to have lower rates of BPD, but this evidence is limited. Treatment of RDS with surfactant replacement therapy theoretically would prevent BPD; however, clinical trials have not shown this long-term benefit (Answer D is incorrect). Early dexamethasone therapy (within 96 hours of birth) has been shown to significantly decrease the incidence of BPD. Unfortunately, long-term follow-up studies showed an increased risk

of cerebral palsy and developmental delay. Until further studies investigating lower doses and optimal timing of dexamethasone are completed, early use of systemic corticosteroids for the prevention of BPD should not be recommended (Answer C is incorrect). Caffeine initiated within 3 days of age has been shown to reduce BPD without negative effects on neurodevelopmental outcomes (Answer B is correct).

3. Answer: D

In clinical practice, long-term therapies for the treatment of BPD are often prescribed. However, there is no evidence to support the use of scheduled bronchodilators, inhaled corticosteroids, or scheduled diuretics in this patient population. None of these therapies have been shown to provide a long-term benefit such as decreased need for mechanical ventilation, length of hospital stay, or mortality in infants with BPD (Answers A–C are incorrect). Symptomatic treatment with as-needed bronchodilators for acute bronchospasm or intermittent doses of diuretic for pulmonary edema provide short-term relief of symptoms without chronically exposing the infant to drugs that have significant potential to cause adverse effects (Answer D is correct). Trial of a short course of low-dose dexamethasone may be warranted at this time to facilitate extubation, given that extubation has failed on several previous attempts.

4. Answer: A

Apnea of prematurity typically resolves by 34–36 weeks' postmenstrual age. Most institutions would not discharge an infant home on methylxanthines if he were still having apnea because the risk of sudden infant death, in the absence of a well-established home monitoring program, is a concern. If apnea has resolved, continuing methylxanthine therapy as an outpatient exposes the infant to possible adverse effects without benefit (Answer D is incorrect). Because this patient has been apnea free since extubation and is older than 36 weeks' postmenstrual age, methylxanthine therapy can be discontinued (Answer A is correct). There is no need to taper caffeine (Answer B is incorrect). Because caffeine has a long half-life, the infant should be monitored for 5–7 days to ensure that he remains apnea free after the drug has been sufficiently cleared from the body. Switching to theophylline offers no advantages; rather, it has several disadvantages, most notably a narrower

therapeutic index, which increases the risk of adverse effects and necessitates the monitoring of serum drug concentrations (Answer C is incorrect).

5. Answer: C

The need for and the timing of pharmacologic closure of the PDA are somewhat controversial. Early therapy (within 3 days of life) is likely to result in overtreatment because many PDAs will spontaneously close. Most clinicians would agree that a PDA should be closed when it manifests with symptoms of significant respiratory deterioration or heart failure. This patient's status has worsened significantly enough to warrant PDA closure with indomethacin (Answer C is correct). Although indomethacin prophylaxis decreases the incidence of symptomatic PDA, it is not 100% effective in doing so, and it is not generally recommended for this indication. Failure of indomethacin prophylaxis to prevent a symptomatic PDA does not indicate the need for a different agent to treat the PDA (Answer A is incorrect). Limited evidence supports the efficacy of acetaminophen for PDA closure, but this agent is not routinely recommended as first-line therapy. In practice, clinicians may use acetaminophen when NSAIDs are contraindicated or if the PDA failed to close with NSAID treatment. Fluid restriction can be adequate to facilitate PDA closure, especially early on; however, it is unlikely to be effective as the sole intervention in an extremely premature neonate. In addition, further fluid restriction in a hypotensive patient whose fluid intake is already limited may worsen hypotension and end-organ perfusion (Answer D is incorrect). Similarly, furosemide administration could worsen hypotension. Furosemide has also been shown to increase renal prostaglandin production; therefore, it is postulated that this agent can contribute to the patency of the ductus arteriosus (Answer B is incorrect).

6. Answer: B

The bacterial pathogens associated with NEC include Enterobacteriaceae (e.g., *E. coli*, *Klebsiella* spp.), *Enterococcus* spp., *Staphylococcus* spp., *Clostridium*, and *P. aeruginosa*, among others. There is no evidence to support the superiority of one antibiotic regimen to others. Selection of the specific agents should be based on the most likely infecting organisms and the individual NICU's susceptibilities. Very broad-spectrum agents (e.g., imipenem) should be avoided unless susceptibility patterns warrant their use (Answer D is

incorrect). A combination of ampicillin and gentamicin lacks the necessary anaerobic coverage recommended for cases of NEC with intestinal perforation and/or peritonitis (Answer A is incorrect); however, adding metronidazole to this combination provides the necessary antibacterial coverage (Answer B is correct). Piperacillin/tazobactam provides anaerobic coverage, so adding metronidazole is unnecessary (Answer C is incorrect). Piperacillin/tazobactam is not generally recommended as a first-line agent because its enterococcal coverage is not as good as that of ampicillin or vancomycin, and its extended gram-negative coverage may not be needed (unless dictated by an individual NICU's susceptibility patterns).

7. Answer: B

There is no evidence-based treatment algorithm for PPHN; therefore, the place in therapy for the various available drugs is unclear; however, inhaled nitric oxide is considered the drug of choice (Answer B is correct). Alternatively, some institutions use inhaled prostacyclin analogs preferentially because of lower cost and evidence of similar efficacy to inhaled nitric oxide. Neonates with PPHN who are treated with inhaled nitric oxide have been found to have increased PDE-3 activity. Milrinone is a PDE-3 inhibitor that augments the pulmonary vasodilation of inhaled nitric oxide. In addition, milrinone has inotropic and lusitropic effects that would be expected to improve right ventricular function; however, given the availability of targeted therapies, it is not used as first-line monotherapy. (Answer C is incorrect). The absorption of oral medications (i.e., sildenafil and bosentan) is unlikely to be reliable because of the severity of this patient's illness and the reduced perfusion to the GI tract (Answer A is incorrect). Sildenafil administered as an intermittent intravenous infusion has been reported in neonates with PPHN, but data are insufficient regarding its optimal dosing to recommend it routinely (Answer D is incorrect).

8. Answer: C

The AAP has published a treatment algorithm for asymptomatic neonates born to mothers with visible genital HSV lesions. Because this neonate's surface cultures were positive for HSV, acyclovir cannot be discontinued (Answer A is incorrect). The neonate's CSF HSV PCR is negative, but her serum ALT is more than 2 times the upper limit of normal. This rules out CNS involvement but confirms disseminated disease.

Therefore, she should receive therapy with intravenous acyclovir for proven disease. The recommended duration for disseminated disease is a minimum of 21 days (Answer C is correct). If she had developed only skin lesions (SEM disease), she would be treated with intravenous acyclovir for 14 days (Answer B is incorrect). Oral acyclovir is recommended for suppressive therapy after intravenous acyclovir treatment of SEM, CNS, or disseminated disease, but it is not indicated for the initial treatment of HSV infection (Answer D is incorrect).

9. Answer: C

The AAP has published a treatment algorithm for neonates born to mothers with reactive serologic tests for syphilis. This neonate is at minimal risk of syphilis because the mother received adequate treatment (i.e., penicillin given more than 4 weeks before delivery), the neonate's RPR titer is not greater than 4-fold the mother's titer (i.e., it is the same), the mother shows no signs of relapse/reinfection, and the neonate is asymptomatic. However, because adequate maternal treatment can still result in failure to prevent congenitally acquired syphilis, treatment is indicated (Answer A is incorrect). According to the algorithm, aqueous penicillin G is the preferred treatment of syphilis, even if ampicillin was started initially for ruling out sepsis, because the efficacy of ampicillin for treating congenital syphilis is unknown (Answer B is incorrect). Benzathine penicillin G is the recommended treatment for neonates born to mothers treated with penicillin more than 4 weeks before delivery but during the pregnancy AND if the neonate has a normal physical examination and an RPR/VDRL titer is the same as or less than 4-fold the mother's titer (Answer C is correct). Close follow-up should be ensured if a single-dose treatment option is used. Longer treatment durations (e.g., aqueous penicillin G x 10 days) are recommended if the neonate's RPR titer is greater than 4-fold the mother's titer or if the neonate's evaluation is abnormal (Answer D is incorrect). In this case, the neonate's initial respiratory symptoms most likely occurred because of transient tachypnea of the newborn, rather than sepsis or pneumonia, because they resolved quickly; this, in conjunction with blood cultures that are negative at 48 hours, makes it reasonable to discontinue ampicillin and gentamicin.

10. Answer: A

This infant is at high risk of developing NAS because of in utero exposure to methadone. When using the

Finnegan scoring tool to assess neonates at risk of withdrawal, three consecutive scores of 8 or higher or two consecutive scores of 12 or higher indicate the need for pharmacologic management of withdrawal (Answer A is correct). Lower scores may indicate mild withdrawal symptoms that should be managed with nonpharmacologic interventions (e.g., swaddling; minimal handling; reduced environmental noise; subdued lighting; frequent, small feedings). Although this neonate is not currently showing severe signs of withdrawal requiring pharmacologic intervention, she should continue to be monitored because withdrawal from methadone typically manifests on days 2–6 of age (Answers B–D are incorrect). If severe withdrawal does occur, an opioid agent (e.g., morphine, methadone) is the treatment of choice. Clonidine is an effective adjunctive therapy with morphine. Phenobarbital is not as effective for monotherapy as an opioid agent because phenobarbital does not treat the GI symptoms or seizures.

11. Answer: C

The current FDA pregnancy categories do not provide a scale of risk (i.e., the risk of harm does not increase from category A to category X). These pregnancy categories only provide information on whether evidence that exposure to the drug during pregnancy, in animals and/or humans, has been associated with fetal harm (Answer A is incorrect). For example, the main difference between category B and category C is that animal studies have not shown fetal harm for drugs categorized as B, whereas animal studies have shown harm for drugs in category C. It is important to recognize that harm in animals does not always translate to the same effect in humans. Neither category contains information regarding the safety in pregnant humans. The current categories also do not consider the severity, treatability, or reversibility of fetal harm, so drugs in the same category can cause very different degrees of harm—what is the same within the category is the type of evidence supporting whether harm occurs (Answer B is incorrect). In addition, the pregnancy categories address only the potential risk to the fetus from drug exposure. They do not consider the risk to the fetus or mother if the mother's condition is untreated (Answer D is incorrect). Overall, drugs from any category, except for category X, may be reasonable treatment options for a pregnant woman (Answer C is correct). When determining which drug to use in a pregnant woman, the clinician must evaluate many factors, including

the specific teratogenic/fetotoxic effects, their incidence (if known), and the mother's medical history (i.e., current diagnoses and medications), and must weigh the potential benefits of treatment against the risks to the fetus from drug exposure as well as the risk of not treating. For these reasons, the current pregnancy categories are not very helpful clinically, and a new system has been proposed.

12. Answer: C

When assessing whether a drug is safe for administration during lactation, several factors must be considered: The molecular weight, protein binding, half-life, and oral bioavailability of the drug can affect the transfer of the drug into the breast milk and the subsequent oral absorption by the infant; the maternal

serum concentration can affect the concentration in the breast milk; potential adverse effects of the drug in the infant; and the risk-benefit of continuing breastfeeding during therapy. The likelihood of significant maternal serum concentrations of tobramycin after ophthalmic administration is very low. Similarly, tobramycin's oral bioavailability is very low; therefore, the amount of drug available to the infant and the extent to which it is absorbed will not lead to a significant exposure (Answer A is incorrect; Answer C is correct). Because tobramycin exposure is likely to be low from breastfeeding, GI flora should not be altered; therefore, probiotics would not be of benefit (Answer D is incorrect). "Pumping and dumping," which eliminates all the benefits of breastfeeding, is generally not recommended (Answer B is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

Although all of the stated properties of a surfactant product would potentially be advantageous, a product that affects long-term outcomes (e.g., reducing the incidence of BPD) would be the most beneficial (Answer D is correct). Surfactant protein B is known to be a critical component of endogenous surfactant; however, exogenous products with higher SP-B content have not been shown consistently to result in better long-term outcomes (Answer A is incorrect). A rapid onset of action may result in the ability to wean oxygen more rapidly and a shorter duration of mechanical ventilation, but these short-term improvements have not translated into long-term benefit (e.g., decreased length of hospital stay, reduced risk of BPD, reduced mortality) (Answers B and C are incorrect). In fact, a very rapid onset may increase the risk of adverse effects (e.g., pneumothorax) if vigilant adjustments are not made to the patient's mechanical ventilator settings shortly after surfactant administration.

2. Answer: C

Case reports and case series are known to be subject to publication bias because of the desire to report positive results and to be less likely to report inconclusive or negative results, thus, a case series reporting the 100% efficacy of acetaminophen for PDA closure (Answer C is correct). Heterogeneity between comparator groups can also lead to disparate results; however, in this example, it is not the most likely cause because most neonates treated for PDA are premature, the timing of the treatments was similar in the two publications, and both publications examined the efficacy of a first course of treatment—all major factors that could confound the results if they differed between the groups (Answer A is incorrect). An inadequate statistical power results in the failure to find a difference between treatments when a difference actually exists and often results from an inadequate sample size. This concept applies to a single study comparing two or more treatment groups, but it cannot be applied when comparing results from different studies (Answer B is incorrect). Superiority of one treatment to another can be concluded only from head-to-head comparison studies designed to detect this difference. Superiority cannot be proved in studies designed to find noninferiority, nor can it be concluded from comparing the results of separate publications (Answer D is incorrect).

3. Answer: D

Clinical trials have shown that indomethacin prophylaxis for IVH reduces the incidence of severe IVH (i.e., grades III and IV). For this reason, some NICUs have implemented an IVH prophylaxis protocol using indomethacin in premature neonates (Answer D is correct). The trials also showed a reduced incidence of PDA; however, this finding does not justify the use of indomethacin for prophylaxis. Many PDAs will close spontaneously, so the benefit of preventing them by exposing neonates to a drug that ultimately may not have been needed does not justify the risk of adverse effects from this intervention (Answer C is incorrect). The trials have not shown a reduction in mortality or improved neurodevelopmental outcome (Answers A and B are incorrect). Some clinicians would argue that this lack of long-term benefit suggests that indomethacin prophylaxis should not be routinely used.

4. Answer: A

Tachycardia is a well-known adverse effect of both theophylline and caffeine therapy (Answer A is correct). Unlike theophylline, caffeine has a wide therapeutic range, and serum concentrations have not been shown to correlate well with efficacy or toxicity. Therefore, routine monitoring of caffeine serum concentrations is not recommended (Answer C is incorrect). Methylxanthine therapy has been associated with decreased lower esophageal sphincter tone, which, some investigators have theorized, increases episodes of gastroesophageal reflux. However, a causative relationship has not been clearly defined, and the more likely cause of reflux episodes in a preterm neonate is immaturity of the lower esophageal sphincter and poor GI motility (Answer D is incorrect). Physiologic gastroesophageal reflux is common in this patient population. Methylxanthine therapy is not known to be nephrotoxic (Answer B is incorrect).

5. Answer: A

According to AAP recommendations, a neonate with a birth weight of at least 2000 g who is born to a mother with an unknown HBsAg status should receive the hepatitis B vaccine within 12 hours of birth. Administration of HBIG can be delayed for up to 7 days after birth, awaiting the mother's test results (Answer A is correct). If, at that time, the mother's status is still unknown or is positive, HBIG should be administered (Answers

C and D are incorrect). Administration of both agents within 12 hours of birth is recommended if the mother's HBsAg is positive or for neonates with a birth weight less than 2000 g who are born to mothers whose HBsAg status is unknown (Answer B is incorrect).

6. Answer: D

This neonate's presentation is consistent with disseminated herpes disease because she has lesions in her mouth and positive herpes PCR from the CSF. According to the AAP treatment algorithm, intravenous acyclovir should be administered for at least 21 days for disseminated or localized CNS disease (Answer D is correct; Answers A–C are incorrect). Near the end of 21 days of treatment, the CSF PCR should be repeated to confirm the clearance of HSV. If the PCR is negative, acyclovir can be discontinued after 21 days of therapy. If the PCR is positive, acyclovir should be continued for an additional 7 days, after which the CSF PCR should be rechecked; acyclovir should be continued until the PCR is negative. Shorter courses of acyclovir are recommended for preemptive therapy without proven disease (10 days) and for SEM disease (14 days).

7. Answer: D

There are several biologically plausible theories for the prevention of BPD by various drug therapies. Because *Ureaplasma* spp. have been isolated from the tracheal aspirates of neonates with BPD, it has been theorized that eliminating that organism will decrease the incidence of BPD. Clinical trials have not shown this benefit in all neonates at high risk of BPD (Answer A is incorrect). When examining a specific subset of neonates proven to be colonized with *Ureaplasma*, azithromycin initiated within 3 days of birth did reduce the incidence of BPD. A PDA with a left-to-right shunt increases pulmonary blood flow and is a risk factor for developing BPD; therefore, theoretically preventing a PDA would decrease the risk of BPD. This has not been shown to be true with indomethacin or ibuprofen prophylaxis or with PDA treatment (Answer B is incorrect). In animal models, inhaled nitric oxide has been shown to reduce lung inflammation and promote lung growth that would theoretically decrease the risk of BPD. Clinical trials of human neonates have not shown this benefit (Answer C is incorrect). Vitamin A has been shown to reduce the incidence of BPD in clinical trials (Answer D is correct). Although used in some NICUs, vitamin A has not become a standard of care within neonatology, given

concerns about frequent intramuscular injections in extremely premature neonates as well as a lack of evidence showing a long-term benefit in improving neurodevelopmental outcomes.

8. Answer: B

Although oral probiotics are not considered the standard of care for preventing NEC, many studies show their efficacy of doing so. The optimal duration is unknown, but a recent study showed a benefit in neonates receiving oral probiotics until 34 weeks' postmenstrual age (Answer B is correct). Other positive studies continued this intervention until the neonate reached term corrected age or until hospital discharge. Delaying enteral feeding has been theorized to reduce the incidence of NEC because it allows for the maturation of the GI tract, and cases of NEC rarely occur in neonates who have not been fed enterally. Overall, clinical studies have not shown this benefit (Answer A is incorrect). Administration of oral antibiotics has been shown to reduce NEC, but the benefit of this intervention is outweighed by the risk of colonization with resistant organisms, which is an outcome that has occurred in clinical trials (Answer C is incorrect). Administration of histamine-2 receptor antagonists has been associated with an increased incidence of NEC. Increasing the pH of the GI tract allows the overgrowth of bacteria, so this intervention should be avoided (Answer D is incorrect).

9. Answer: B

Three consecutive scores using the Finnegan tool of 8 or higher or two consecutive scores of 12 or higher are indicative of the need for pharmacologic management of withdrawal (Answer D is incorrect). An opioid agent (e.g., morphine, methadone) is the treatment of choice for managing withdrawal symptoms from hydrocodone exposure (Answer B is correct). Clonidine is generally reserved for adjunctive therapy with morphine (Answer A is incorrect). Phenobarbital monotherapy is not as effective as morphine or methadone for managing opioid withdrawal because it does not treat the GI symptoms or prevent seizures (Answer C is incorrect). Phenobarbital is often used as first-line monotherapy for withdrawal from non-opioid agents.

10. Answer: C

Drug characteristics associated with transport across the placenta include low molecular weight (less than 500 Da), lipophilicity, and low protein binding (Answer

C is correct; Answers A and B are incorrect). A prolonged half-life may increase the time during which the drug can cross the placenta but, without the other characteristics, does not alone promote drug transport across the placenta (Answer D is incorrect). Although transfer across the placenta does not necessarily predict a drug's teratogenicity, it is required for the drug to cause fetal harm.

11. Answer: B

Group B *Streptococcus*, *E. coli*, and *Listeria* are all common pathogens causing early neonatal sepsis (Answer B is correct; Answers C and D are incorrect). *C. albicans* can cause late-onset neonatal sepsis, especially in neonates with specific risk factors (e.g., history of abdominal surgery, long-term total parenteral nutrition, *Candida* colonization of several sites) (Answer A is incorrect). However, because *E. coli* is most likely to be associated with NEC, it should be covered by an empiric antibiotic regimen—most commonly with an aminoglycoside or a third- or fourth-generation cephalosporin.

12. Answer: D

Drugs that are not highly protein bound or that have long half-lives are more likely to be transferred into and accumulate in breast milk than are those that are highly protein bound or have shorter half-lives, thus increasing the potential for neonatal exposure and adverse effects (Answers A and B are incorrect). In theory, breastfeeding when maternal serum concentrations are likely to be the lowest during the day would minimize exposure to the neonate. However, in reality, this is not very feasible because most neonates feed at least six to eight times a day; thus, maternal serum concentrations would not be low at most of the feeding times (Answer C is incorrect). Maternal serum concentrations do have a significant effect on the concentration of drug in the breast milk, so treating the mother with the lowest effective dose would result in a lower concentration and therefore decrease overall drug exposure to the neonate (Answer D is correct).

13. Answer: C

Inhaled nitric oxide is the treatment of choice for PPHN (Answer C is correct). Beractant may be a reasonable adjunctive therapy because meconium aspiration can result in endogenous surfactant inactivation, but it is not a pulmonary vasodilator (Answer A is incorrect).

Similarly, vecuronium may be added as supportive therapy if the patient does not respond adequately to sedation and pain management, but it will not produce pulmonary vasodilation (Answer D is incorrect). Epoprostenol is a pulmonary vasodilator, but it is considered an additive therapy if the response to nitric oxide is inadequate. Its more invasive route of administration (i.e., intravenous vs. inhaled), risk of systemic hypotension, and relative lack of supporting literature compared with inhaled nitric oxide make epoprostenol a second-line therapy for PPHN (Answer B is incorrect).

ENDOCRINE DISORDERS

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ENDOCRINE DISORDERS

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Learning Objectives

1. Given a specific patient, design or evaluate the effectiveness of a management regimen to optimize glycemic control in a child with diabetes mellitus.
2. Identify classifications and treatment strategies for obesity in children.
3. Develop a treatment strategy for thyroid disorders in children.
4. Differentiate between various treatments for disorders of water metabolism and other metabolic disorders in children.

Abbreviations in This Chapter

ADA	American Diabetes Association
ADR	Adverse drug reaction
ADH	Antidiuretic hormone
BMI	Body mass index
BSA	Body surface area
DI	Diabetes insipidus
DKA	Diabetic ketoacidosis
eGFR	Estimated glomerular filtration rate
GI	Gastrointestinal
I:CHO	Insulin/carbohydrate ratio
ISF	Insulin sensitivity factor
MDI	Multiple daily injection
NPH	Neutral protamine Hagedorn
RAI	Radioactive iodine
SIADH	Syndrome of inappropriate antidiuretic hormone
TDD	Total daily dose
T ₃	Triiodothyronine
T ₄	Thyroxine
TSH	Thyroid-stimulating hormone

Self-Assessment Questions

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

1. You are asked to develop an initial insulin treatment plan with 0.5 unit/kg/day. The patient is an 11-year-old girl (weight 30 kg) with a recent diagnosis of type 1 diabetes. Her diet is consistent. Which insulin regimen would be most appropriate to initiate in this patient?
 - A. Insulin glargine 15 units subcutaneously once daily in the morning and regular insulin 5 units 30 minutes before each meal.
 - B. Neutral protamine Hagedorn (NPH) insulin 7 units and insulin lispro 3 units subcutaneously 30 minutes before the morning meal and NPH 3 units and insulin lispro 1.5 units subcutaneously 30 minutes before the evening meal.
 - C. Insulin detemir 7.5 units subcutaneously once daily in the morning and 2.5 units insulin glulisine subcutaneously 15 minutes before each meal.
 - D. Insulin glargine 7.5 units subcutaneously once daily in the morning and insulin aspart 2.5 units subcutaneously 15 minutes before each meal.
2. H.M. is a 16-year-old male adolescent (body mass index [BMI] 32 kg/m², greater than the 95th percentile for age) who received a diagnosis of type 2 diabetes 3 months ago, after which his primary care physician initiated lifestyle modifications and metformin 500 mg twice daily. At diagnosis, his hemoglobin A1C concentration was 8.5%. Last week, his A1C concentration was 7.7%. He states that his fasting glucose concentrations during the past 1–2 weeks have been 145–190 mg/dL. He states that he is tolerating the metformin well. Which would be the most appropriate treatment option for H.M. at this time?
 - A. Add exenatide 5 mcg subcutaneously twice daily.
 - B. Increase metformin dose to 1000 mg twice daily.
 - C. Discontinue metformin and initiate pioglitazone 15 mg daily.
 - D. Add insulin aspart 5 units subcutaneously 15 minutes before meals.

3. A 13-year-old female adolescent with type 1 diabetes currently takes glargine 20 units at bedtime plus aspart 5 units before meals. Given her blood glucose monitoring results below and the absence of nocturnal hypoglycemia, which regimen change would most appropriately address her elevated blood glucose readings?

	Morning Preprandial	Noon Preprandial	Evening Preprandial	Bedtime Preprandial
Range	150–200	190–235	95–120	110–130
Average	175	215	100	115

- A. Glargine 20 units at bedtime plus aspart 7 units before breakfast plus aspart 5 units before lunch and supper.
- B. Glargine 22 units at bedtime plus aspart 7 units before breakfast plus aspart 5 units before lunch and supper.
- C. Glargine 22 units at bedtime plus aspart 5 units before meals.
- D. Glargine 22 units at bedtime plus aspart 7 units before meals.
4. A 6-year-old child (weight 17 kg, body surface area [BSA], 0.9 m²) is given a diagnosis of central diabetes insipidus (DI). Which is the most appropriate initial treatment?
- A. Desmopressin 0.05 mg orally twice daily.
- B. Hydrocortisone 3 mg orally every 8 hours plus fludrocortisone 0.05 mg orally once daily.
- C. Water restriction of no more than 900 mL/day.
- D. Sapropterin 170 mg orally once daily.
5. A 4-year-old child (weight 12 kg, BSA 0.8 m²) is given a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH). Which is the most appropriate initial treatment?
- A. Desmopressin 0.05 mg orally twice daily.
- B. Hydrocortisone 2 mg orally every 8 hours plus fludrocortisone 0.05 mg orally once daily.
- C. Water restriction of no more than 800 mL/day.
- D. Furosemide 24 mg orally once daily.
6. A 10-year-old (weight 25 kg, BSA 1.4 m²) receives a diagnosis of adrenal insufficiency. Which is the most appropriate initial treatment?
- A. Desmopressin 0.05 mg orally twice daily.
- B. Hydrocortisone 4 mg orally every 8 hours plus fludrocortisone 0.05 mg orally once daily.
- C. Fluid replacement of more than 1400 mL/day.
- D. Sapropterin 120 mg orally once daily.
7. A 12-year-old girl (weight 40 kg) has just been given a diagnosis of Hashimoto disease. Which is the most appropriate initial therapy?
- A. Methimazole 20 mg orally once daily.
- B. Liothyronine 25 mcg orally once daily on an empty stomach.
- C. Levothyroxine 175 mcg orally once daily on an empty stomach.
- D. Iodide 150 mg orally thrice daily in water or juice.
8. A 12-year-old (weight 40 kg) has just been given a diagnosis of Graves disease. Which is the most appropriate initial therapy?
- A. Methimazole 20 mg orally once daily.
- B. Liothyronine 25 mcg orally once daily on an empty stomach.
- C. Levothyroxine 175 mcg orally once daily on an empty stomach.
- D. Iodide 150 mg orally three times daily in water or juice.
9. A 13-year-old male adolescent (BMI 35 kg/m²) has diligently been following an intense lifestyle modification program for 18 months, but he is making no progress. His family is heavily involved and following a similar plan. His obesity is making it difficult to be successful at treating his dyslipidemia and hypertension. Which would be the most appropriate adjunctive therapy to add?
- A. Phentermine 15 mg orally once daily.
- B. Orlistat 120 mg orally with the three big meals a day.
- C. Sibutramine 5 mg orally once daily.
- D. Bariatric surgery.

10. A male patient with type 1 diabetes is on a basal/bolus regimen of 10 units of glargine at bedtime and flexible dosing with aspart using 1:10 for carbohydrates (insulin/carbohydrate ratio [I:CHO]) and 1:50 for corrections (insulin sensitivity factor [ISF]). The patient feels odd and checks his blood glucose, which reads 50 mg/dL on the glucometer. Which is the most appropriate course of action for the patient to take?
- A. Take 1 unit of aspart insulin because the ISF is 1:50.
 - B. Do nothing until the next scheduled meal and injection time.
 - C. Take 15 g of fast-acting sugar and 1 unit of aspart insulin because the I:CHO is 1:15.
 - D. Take 15 g of fast-acting sugar and recheck in 15 minutes.
11. According to the American Diabetes Association (ADA), which blood glucose (plasma) value most accurately depicts the targeted fasting goal for a 14-year-old with type 1 diabetes?
- A. Less than 180 mg/dL.
 - B. 90–150 mg/dL.
 - C. 80–120 mg/dL.
 - D. 90–130 mg/dL.
12. A 4-year-old boy (weight 12 kg, BSA 0.8 m²) has had slow onset of DI symptoms. He did not have a prompt increase in osmolality to the water deprivation test. The patient is being treated for underlying conditions. He is on a diet that maximizes calories while limiting salt intake and currently takes hydrochlorothiazide. He is currently uncontrolled. Which is the most appropriate adjunctive treatment?
- A. Desmopressin.
 - B. Indomethacin.
 - C. Chlorothiazide.
 - D. Amiloride.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

Domain 1: Patient Management; Task(s): 1.2 and 1.4

I. DIABETES MELLITUS

A. Classification

1. Diabetes mellitus is a disease state that results in an inappropriately high amount of glucose circulating in the blood over extended intervals.
2. Type 1 diabetes is a result of insulin deficiency brought on by autoimmune destruction of the insulin production pathways at the beta cells of the pancreas. This is still the most common type in children.
3. Type 2 diabetes is a result of the development of insulin resistance in the body. Insulin production may be normal, increased, or decreased depending on the disease course, but alterations in production are not autoimmune. The incidence has greatly increased in children during the past decades. In some areas, up to 40% of new-onset diabetes is type 2 diabetes.

B. Symptoms

1. Polydipsia
2. Polyuria
3. Polyphagia
4. Weight changes
5. Lethargy
6. Diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar state

C. Screening

1. No routine screening for patients with type 1 diabetes.
2. ADA and American Academy of Pediatrics recommendations for screening for type 2 diabetes. Children who are overweight plus have one or more of the following:
 - a. Family history of type 2 diabetes in a first- or second-degree relative
 - b. Native American, African American, Latino, Asian American, or Pacific Islander
 - c. Has signs of insulin resistance or conditions associated with insulin resistance (e.g., acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome)
 - d. Maternal history of diabetes or gestational diabetes during child's gestation
3. Screening should occur at 3-year intervals, beginning when the child is 10 years old or at the onset of puberty, whichever comes first. Screening should be performed using same types of procedures as used for diagnosis, except for a random plasma glucose (Table 1).
4. Additional recommendations: Children with a BMI at the 95th percentile or higher, regardless of family history or associated features

D. Diagnosis

Table 1. Diagnostic Criteria^a

	Random Plasma Glucose (mg/dL)	Fasting Plasma Glucose (mg/dL)	2-Hr Post-glucose (75 g) Load (mg/dL)	A1C (%)
Prediabetes	—	100–125	140–199	5.7–6.4
Diabetes	≥200 (with symptoms)	≥126	≥200	≥6.5

^aAbnormal result should be repeated on a separate occasion to confirm diagnosis, except in the presence of overt symptoms. It is recommended to use same test to confirm, when possible.

E. Treatment Goals

1. Maintain daily ranges of blood glucose concentrations so that activities of daily living are not inhibited. Ideally, have most concentrations within target ranges.
 - a. For children: Fasting 90–130 mg/dL, bedtime 90–150 mg/dL
 - b. A stepwise approach can be taken with initial goals less stringent to assess the risk of hypoglycemia.
 - i. For children younger than 6 years: Fasting 100–180 mg/dL, bedtime 110–200 mg/dL
 - ii. For children 6–12 years: Fasting 90–180 mg/dL, bedtime 100–180 mg/dL
2. Prevent the occurrence or progression of long-term macrovascular and microvascular complications. Ideally, meet A1C goals.
 - a. For type 1 and type 2, less than 7.0% (ADA and International Society for Pediatric and Adolescent Diabetes [ISPAD])
 - b. Caution is advised to individualize goals according to patient characteristics, especially in children younger than 6 years and who are at a greater risk of hypoglycemia and have poor hypoglycemic awareness.
3. Prevent acute complications.
 - a. Monitor for and proactively address hyperglycemia (pre-DKA) and hypoglycemia.
 - b. Minimize the adverse drug reactions (ADRs) of medications.
4. Screen for and control other comorbidities: hyperlipidemia, hypertension, nephropathy, retinopathy, neuropathy, psychosocial factors, and other classification-specific diseases.
5. Incorporate and foster self-management.
 - a. Age- and ability-appropriate, culturally sensitive self-management goals.
 - b. Meet and support patients' and caregivers' expectations.
 - c. Engagement of parents/caregivers in care and ensuring responsibility prior to transfer of care.

F. Carbohydrate Counting

1. An approach to help patients with diabetes plan meals
2. Regardless of type of diabetes, patients need to be aware of the amount of carbohydrates they eat.
3. Patients count all the carbohydrates in each meal and snack eaten.
4. Patients using flexible dosing may adjust their insulin dose according to the amount of carbohydrates eaten.
5. Allows for better blood glucose control
6. Can be used to follow a structured diet, monitor effects on blood glucose, and adjust medication doses

G. Medication

1. Medications with a U.S. Food and Drug Administration (FDA) indication for use in children with diabetes mellitus
 - a. Insulin: For type 1 and type 2 diabetes
 - b. Metformin: For type 2 diabetes
 - c. Liraglutide: For type 2 diabetes
 - d. Exenatide extended release: For type 2 diabetes
2. Insulin
 - a. Use insulin formulations to mimic the normal physiologic release of insulin.
 - i. Basal insulin matches the homeostatic release of glucose by the liver as a release of small amounts throughout the day.
 - ii. Bolus insulin matches glucose excursions from food absorption and in response to hormonal situations.
 - b. Short-acting insulin: Used primarily to control postprandial hyperglycemia
 - i. Regular human insulin

- ii. Rapid-acting insulin: Onset of activity and time to peak concentration are more rapid and has shorter duration of activity than regular human insulin. This type of insulin also has a time to peak action that is independent of the insulin dose.
 - (a) Insulin glulisine
 - (b) Insulin aspart
 - (1) Available in half-unit dosing pens
 - (c) Insulin lispro
 - (1) Available in half-unit dosing pens
- iii. Short-acting insulin pearls
 - (a) Role is to lower postprandial hyperglycemia (also known as “bolus” insulin).
 - (b) Timing before a meal is important.
 - (1) Optimally, about 5–15 minutes before a meal for rapid-acting insulin
 - (2) Optimally, about 30–60 minutes before a meal for regular human insulin
 - (c) Rapid acting preferred to regular human insulin because of faster onset and shorter duration, better mimicking of physiologic need during postprandial period
 - (d) Fast onset warrants caution with “choosy” eaters. Rapid acting insulins provide similar glycemic control when administered immediately after a meal.
- c. Intermediate-acting insulin is used as adjunctive agent or in specific situations when its action curves fit a need.
 - i. NPH
 - (a) Older insulin formulation that offers both basal and bolus coverage during its release period; however, does not match the physiologic need of either well
 - (b) Morning NPH is used to offer some morning basal coverage and to lower glucose concentrations after lunch.
 - (c) Evening NPH is used to offer overnight basal coverage and to lower glucose concentrations associated with increased liver release in early morning.
 - ii. Intermediate-acting insulin pearls
 - (a) NPH is a cloudy suspension and can be mixed with regular or rapid acting
 - (1) The short-acting insulin should always be obtained first. This is to avoid potential contamination by NPH, which could alter the insulin action release curve of the short-acting insulin.
 - (2) Sometimes called “clear before cloudy”
 - (b) Variability in action curve from dose to dose
- d. Long-acting insulin: Used primarily as basal coverage for nonprandial glucose release
 - i. Insulin glargine
 - ii. Insulin detemir
 - iii. Insulin degludec
 - iv. Long-acting insulin pearls
 - (a) Glargine
 - (1) Improved glucose control compared with NPH
 - (2) May decrease hypoglycemic events
 - (3) Essentially peakless in most patients
 - (4) Cannot mix with other insulins
 - (5) Injection-site reactions (e.g., edema, itching, pain, stinging). Because of acidic formulation, a burning sensation may be more pronounced than that with other insulin injections.
 - (6) Toujeo is a new formulation available as a U300 concentration in a disposable pen.

- (b) Detemir
 - (1) Dose-dependent duration of action
 - (2) Doses less than 0.4 unit/kg usually will not last 24 hours; doses of 0.2 unit/kg or less must be given twice daily to achieve 24 hours of control.
 - (3) Smoother activity profile compared with NPH and glargine
 - (4) Less weight gain compared with NPH and glargine
 - (5) Decreased hypoglycemia compared with NPH
 - (6) Cannot mix with other insulins
 - (7) Injection-site reactions (e.g., edema, itching, pain, stinging)
- (c) Degludec
 - (1) Lasts 42 hours but given once daily. There will be a stacking effect, so it takes 3–4 days to reach a steady state.
 - (2) Do not make dose adjustments sooner than 3–4 days.
 - (3) Extended duration allows greater flexibility in dosing time. Daily dose does not have to be given at the same time each day. A delayed dose does not result in a basal free period. A missed dose can be given when recognized if it is not within 8 hours of next dose.
 - (4) Comes in pens of two concentrations with no dose conversions needed
 - (A) U100
 - (B) U200
 - (5) Cannot mix with other insulins
- e. Table 2 has approximate values for subcutaneous delivery of available insulins. Some variation will occur, depending on the individual patient, injection location, and subcutaneous fat consistency.

Table 2. Insulin Action

Insulin	Onset	Peak	Duration
Lispro (Humalog) (Admelog)	5–15 min	0.5–2 hr	3–5 hr
Aspart (NovoLog)	5–15 min	1–2 hr	3–5 hr
Aspart (Fiasp)	2.5–10 min	0.5–1.5 hr	3–5 hr
Glulisine (Apidra)	15–20 min	0.75–1 hr	4–5 hr
Regular (Humulin R, Novolin R)	30–60 min	2–4 hr	4–8 hr
Neutral protamine Hagedorn	1–2 hr	5–10 hr	10–16 hr
Detemir (Levemir)	1–2 hr	4–8 hr	10–24 hr
Glargine (Lantus) (Basaglar) (Semglee)	2 hr	2–4 hr	20–24+ hr
Glargine (Toujeo U300)	6 hr	Peakless	24–36 hr
Degludec (Tresiba)	1 hr	9–12 hr	42 hr

3. Metformin

- a. The only oral drug labeled for use in the treatment of type 2 diabetes in children; available as oral solution, tablet, and extended-release tablet
- b. Inhibits hepatic glucose production and release
- c. For children at least 10 years of age, recommended maximal daily dose is 2000 mg.
- d. Adverse gastrointestinal (GI) effects and weight loss are common. Dose titration is recommended to develop tolerance.

- e. Traditionally contraindicated for patients with serum creatinine of 1.5 mg/dL or greater in male patients or 1.4 mg/dL or greater in female patients. The FDA recommends the use of glomerular filtration rate estimating equation (eGFR).
 - i. Contraindicated in patients with an eGFR less than 30 mL/minute/1.73 m²
 - ii. Initiating in patients with an eGFR of 30–45 mL/minute/1.73 m² is not recommended.
 - f. Boxed warning for lactic acidosis. Risk increases in patients with severe renal impairment, which can lead to an accumulation of metformin in the blood. It is also increased in patients with heart failure and other conditions that can lead to hypoxemia and hypoperfusion. This warning is based on adult data.
 - g. Vitamin B₁₂ concentrations may be decreased (based on adult data).
 - h. Has been shown to benefit some adolescents with type 1 diabetes as an adjunct to insulin therapy
4. Glucagon-like peptide-1 receptor agonist (GLP-1)
- a. An analog of human GLP-1 that increases insulin release, decreases glucagon secretion, and can delay gastric emptying
 - b. For children at least 10 years of age
 - c. Contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.
 - d. Adverse GI effects and weight loss are common. Dose titration is recommended to develop tolerance. Possible serious adverse effects include risk of thyroid C-cell tumors, pancreatitis, and hypoglycemia.
 - e. Liraglutide
 - i. Approved by the FDA in 2019 and available as an injectable pen in doses of 0.6 mg, 1.2 mg, and 1.8 mg
 - f. Exenatide extended release
 - i. Approved by the FDA in 2021, a once weekly injection available as a 2 mg dose in either a single dose tray or a single dose injectable pen. Both require mixing prior to injection.

H. Type 1 Diabetes Management

1. Basal/bolus (basal/prandial) insulin regimen is recommended.
 - a. Multiple daily injection (MDI) regimen
 - b. Subcutaneous insulin pump regimen
2. MDI regimen of 4 or more injections per day
 - a. Consists of a long-acting insulin for basal coverage and a short-acting insulin for bolus coverage
 - b. Advantages
 - i. Meal times can vary.
 - ii. Carbohydrate intake can vary.
 - iii. Less insulin overlap
 - iv. Usually best injectable option for blood glucose control because it closely mimics physiologic insulin release
 - v. Less blood glucose variability
 - c. Disadvantages
 - i. Several injections each day
 - ii. May be difficult for some patients because of the math and problem solving required for flexible dosing
 - iii. More costly than an NPH regimen
3. MDI regimen of 2 injections per day with NPH
 - a. A short-acting insulin is used as bolus coverage for breakfast and dinner. NPH is used as both basal coverage and bolus coverage for lunch. Mixing the two insulins together in a syringe results in single injections at breakfast and dinner.

- b. Advantages
 - i. Only 2 injections each day
 - ii. No injections at school for lunch
 - iii. Less chance of forgetting
 - iv. Easier to learn fixed dosing than MDI flexible dosing
 - v. Less expensive
 - c. Disadvantages
 - i. Does not mimic physiologic release of insulin well
 - ii. Requires meals to be at specific times
 - iii. Requires constant/consistent carbohydrate intake
 - iv. Snacks needed
 - v. Greater risk of hypoglycemia, especially overnight
 - vi. Difficult to achieve treatment goals
4. MDI regimen of 3 injections per day with NPH
- a. Adaptation of 2-injection NPH regimen. Only the breakfast injection contains short-acting insulin and NPH insulin. Short-acting insulin only is used at dinner, and the evening NPH injection is moved to bedtime. This is done to better match overnight glucose release by the liver.
 - b. Advantages
 - i. Decreases the risk of overnight hypoglycemia compared with the 2-injection NPH regimen
 - ii. Fewer than 4 injections a day
 - iii. Better control of dawn phenomenon than the 2-injection NPH regimen
 - iv. No midday injection for food; however, a correctional dose may be needed at times
 - c. Disadvantages
 - i. Requires meals to be at specific times
 - ii. Requires constant/consistent carbohydrate intake
 - iii. Snacks needed
 - iv. More than 2 injections daily
 - v. Difficult to achieve treatment goals
 - d. Example of situation in which use would be appropriate: Patient on 2-injection regimen has lower blood glucose concentrations (60–90 mg/dL) around midnight, but blood glucose then climbs to the high 200s by the morning before breakfast. By moving the NPH injection to bedtime, the peak effect is moved to past midnight, possibly leveling off blood glucose values.
5. Initiating insulin
- a. Estimate the patient's total daily dose (TDD) insulin requirement. Initially, 0.3–0.5 unit/kg/day (may consider initial dosing as high as 0.5–1 units/kg/day during puberty)
 - b. Insulin dosing: NPH 2- or 3-injection regimen
 - i. Give two thirds of TDD in the morning.
 - (a) Two thirds as NPH
 - (b) One third as short acting
 - ii. Give one third of TDD in the evening.
 - (a) Two thirds NPH, one third short acting, or
 - (b) Half NPH, half short acting
 - iii. NPH example with TDD of 15 units
 - (a) Calculate two thirds of TDD for the morning: $2/3 \times 15 \text{ units} = 10 \text{ units}$.
 - (b) Calculate two thirds of that morning dose as NPH, one third as short acting
 - (1) $2/3 \times 10 \text{ units} = 7 \text{ units}$ (NPH)
 - (2) $1/3 \times 10 \text{ units} = 3 \text{ units}$ (short)
 - (3) Morning insulin dose: 7 units of NPH and 3 units of short insulin

- (c) Calculate one third of TDD for the evening: $1/3 \times 15 = 5$ units
 - (d) Calculate two thirds as NPH, one third as short, *or* 50/50: 3 units of NPH and 2 units of short or 3 units of NPH and 3 units of short
- c. Insulin dosing: basal/bolus regimen (4 or 4+ injection regimen)
 - i. Long-acting insulin
 - (a) About 50% of TDD. New onsets and small children may require as little as 30% TDD for basal coverage.
 - (b) Example of glargine dose for TDD of 15 units: 50% of 15 units/day = 7.5 units.
 - ii. Short-acting insulin
 - (a) It is recommended to match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity.
 - (b) Fixed dosing for the bolus component can be achieved by simply dividing the remaining percentage of TDD between meals equally. However, this requires the patient to follow a strict carbohydrate intake at each meal to achieve a good match to physiologic need. This may be challenging for children and their families to adhere to.
 - (c) Flexible dosing allows patients to adjust the short-acting insulin dose according to predicted needs. It offers proactive adjustments rather than retroactive “fixes” and gives patients more control and freedom.
 - (1) Uses an I:CHO with an ISF, also known as the *correction factor*
 - (2) I:CHO is the amount, in grams of carbohydrates, covered by 1 unit of insulin. Used to calculate bolus insulin for meals
 - (3) Example: A carbohydrate ratio of 1:15 means that 1 unit of insulin will displace 15 g of carbohydrates. For every 15 g of carbohydrates the meal contains, the patient must inject 1 unit of insulin. For a meal of 30 g, the patient would need to take 2 units of insulin.
 - (4) ISF, or correction factor, is the amount of reduction in blood glucose per 1 unit of insulin. It is used to correct high blood glucose readings in addition to normal bolus insulin for food and to lower blood glucose to a specified target amount
 - (5) Example: ISF of 50 (1:50) means that 1 unit of insulin will reduce blood glucose by 50 mg/dL. For a reading 100 mg/dL above target, patients would need an additional 2 units to lower it to target range.
- d. Initiating an I:CHO
 - i. Can use an insulin/weight-based approach (the rule of 500)
 - ii. Rule of 500
 - (a) $500/\text{TDD} = \text{grams covered by 1 unit of short-acting insulin}$ (some sources recommend using 450 for regular insulin; however, in practice, the resulting doses end up being about the same, regardless of method used)
 - (b) Example: A patient requires 65 units of insulin a day: $500/65 = 7.69$ equals about 7.5, so 1:7.5 I:CHO
- e. Initiating an ISF
 - i. Can use an insulin/weight-based approach (the rule of 1800 for rapid insulin)
 - ii. Rule of 1800
 - (a) $1800/\text{TDD} = \text{mg/dL reduced by 1 unit of rapid-acting insulin}$. For regular insulin, 1500 is used (rule of 1500).
 - (b) For example, a patient requires 65 units of insulin a day: $1800/65 = 27.69$ equals about 30, so 30 ISF (1:30 correction factor)

- f. Example case: A patient is about to eat his lunch, which has 89 g of carbohydrates, and his blood glucose is 210 mg/dL. He uses the following: I:CHO of 1:7.5 and ISF of 30; target of 120.
- i. Food: $89 \text{ (g of carbohydrates)} / 7.5 \text{ (I:CHO)} = 11.86$ equals about 12 units for carbohydrates
 - ii. Correction: $210 - 120 \text{ (target)} = 90 \text{ mg/dL too high}$; $90 / 30 \text{ (ISF)} = 3$ units correction
 - iii. Bolus dose: $12 \text{ (for food)} + 3 \text{ (for correction)} = 15$ units required

Patient Cases

1. A patient presents with type 1 diabetes (weight 60 kg), and you want to initiate a new insulin regimen. You decide to use a 2-injection, NPH plus short-acting regimen. Which represents the most appropriate starting dose?
 - A. 7 units of NPH and 13 units of short acting in the morning plus 5 units of NPH and 5 units of short acting in the evening.
 - B. 7 units of NPH and 7 units of short acting in the morning plus 7 units of NPH and 7 units of short acting in the evening.
 - C. 13 units of NPH and 7 units of short acting in the morning plus 7 units of NPH and 3 units of short acting in the evening.
 - D. 27 units of NPH and 13 units of short acting in the morning plus 13 units of NPH and 6 units of short acting in the evening.
2. A patient presents with type 1 diabetes (weight 60 kg), and you want to initiate a new insulin regimen. You decide to use an intensive basal/bolus glargine/lispro regimen. Which represents the most appropriate starting glargine dose?
 - A. 8 units.
 - B. 15 units.
 - C. 20 units.
 - D. 30 units.
3. A patient presents with type 1 diabetes (weight 60 kg), and you want to initiate a new insulin regimen. You decide to use an intensive basal/bolus glargine/aspart regimen. Which represents the most appropriate starting I:CHO for dosing?
 - A. 1:8.
 - B. 1:15.
 - C. 1:30.
 - D. 1:60.
4. A patient presents with type 1 diabetes (weight 60 kg), and you want to initiate a new insulin regimen. You decide to use an intensive basal/bolus glargine/rapid-acting regimen. Which represents the most appropriate starting ISF for correctional bolus dosing?
 - A. 60 (1:60).
 - B. 30 (1:30).
 - C. 15 (1:15).
 - D. 8 (1:8).

6. Assessment of plan
 - a. Evaluate daily blood glucose records for patterns of poor control. Correlate with A1C data.
 - i. Self-monitored glucose readings should be done a minimum of four to six times daily, including premeal, prebedtime, and for safety concerns with hypoglycemia (e.g., exercise or driving).
 - ii. A1C should be performed every 3 months.
 - b. Assess ability of patient to perform activities of daily living.
 - c. Consider patient and caregiver comfort and satisfaction with the plan.
 - d. Adjust plan to address any issues.
7. Insulin adjustments
 - a. Basal insulin: Adjustments made on the basis of fasting control
 - b. Bolus insulin: Adjustments made on the basis of postprandial and correctional control (ISF)
 - c. Dose of the insulin responsible for area of poor control is usually changed by 10%–20%.
 - d. Fasting control should be targeted first, followed by prandial control and then correctional control.
 - e. Be cautious in increasing insulin for high glucose in the morning before breakfast without overnight blood glucose readings. Early morning hyperglycemia can also be caused by the liver's response to nocturnal hypoglycemia, causing a rebound hyperglycemia (Somogyi effect/phenomenon). This is a result of too much insulin in the evening. In this case, insulin affecting the overnight period should be lowered.

Patient Case

5. A 16-year-old female patient currently takes NPH 20 units plus regular 10 units in the morning and regular insulin 10 units plus NPH 20 units before the evening meal. Given her blood glucose monitoring results below and lack of nocturnal hypoglycemia, which regimen changes would most appropriately address her elevated blood glucose readings?

	Morning Preprandial	Noon Preprandial	Nighttime Preprandial	Bedtime Preprandial
Range	100–120	95–135	160–195	180–230
Average	110	115	175	200

- A. NPH 24 units plus regular 12 units in the morning; regular 10 units plus NPH 20 units in the evening.
- B. NPH 20 units plus regular 10 units in the morning; regular 12 units plus NPH 24 units in the evening.
- C. NPH 20 units plus regular 12 units in the morning; regular 12 units in the evening; NPH 20 units at bedtime.
- D. NPH 24 units plus regular 10 units in the morning; regular 12 units plus NPH 20 units in the evening.

I. Insulin Pumps and Continuous Glucose Monitors

1. Insulin pump: A computerized device that allows both continuous and noncontinuous doses of insulin to be delivered to the body
2. Insulin pumps can administer a subcutaneous basal/bolus regimen using a single short-acting insulin. They release drops of insulin every few minutes to achieve a programmed rate of units per hour, which offers basal control. They use programmed flexible dosing to assist patients in giving bolus doses for food and correction.
3. Advantages
 - a. Smaller dosing increments facilitate more flexibility in dose titration
 - b. Offer the ability to have variable basal release throughout the day
 - c. Allow greater individualization of therapy

- d. Help to adjust for lifestyle variables
 - i. Timing and type of meals
 - ii. Timing and type of exercise
 - e. Allow for tracking of adherence
 - 4. Disadvantages
 - a. More complex
 - b. Require greater diligence and adherence by patient
 - c. Cost
 - 5. Continuous glucose monitor (CGM): A device that measures interstitial fluid glucose concentrations and makes a mathematical prediction of corresponding blood glucose concentrations
 - a. Uses a subcutaneous sensor that sends information by a transmitter to a display device
 - b. Continuous display types that continuously display a reading, show directional trends, and have the ability to alarm on the basis of set ranges
 - c. Intermittent (flash) types that only relay information when a receiving device is placed close to the transmitter and may not offer the benefit of alarms
 - 6. CGMs may be beneficial to children with diabetes, both T1DM and T2DM, as an additional tool for improving glucose control.
 - 7. New device systems that use integrated insulin pumps and CGMs may improve glucose control and reduce hypoglycemia. Newer systems can automatically make small changes to insulin delivery to optimize control and safety.
- J. Type 2 Diabetes Management
 - 1. Treat as type 1 diabetes with a basal/bolus insulin regimen if without definitive classification, pending results from pancreatic autoantibody lab draw or patient presents with DKA and requires hospitalization
 - 2. Treat all patients with metformin unless contraindicated.
 - 3. Add insulin to metformin at diagnosis if A1C is greater than 8.5% or blood glucose concentrations are greater than 250 mg/dL.
 - a. May be basal alone or basal/bolus regimen
 - i. A basal/bolus regimen can be considered if A1C or blood glucose concentrations are high (A1C greater than 10%, blood glucose greater than 350 mg/dL) or if patient has DKA.
 - ii. For this combination regimen, insulin would be initiated the same as in a child with type 1 diabetes.
 - b. Initiate basal-alone regimen at 0.25–0.5 unit/kg.
 - 4. If goals are not met after metformin (with or without basal insulin) is at target dose, consider adding approved GLP-1 receptor agonist.
 - 5. Intensify treatment if blood glucose and A1C goals are not met, adding basal insulin if not already started.
 - 6. Insulin can be tapered over time as control improves and possibly discontinued in some instances.
 - 7. Metabolic surgery may be considered if BMI is greater than 35 kg/m² and patient has uncontrolled glycemia and/or serious comorbidities even with lifestyle and pharmacotherapy management.
- K. Manage Acute Hypoglycemia
 - 1. For blood glucose less than 70 mg/dL, initiate hypoglycemic treatment, 15 g of fast-absorbing carbohydrates.
 - a. Liquid sugars such as fruit juice, flavored sugar and water, or pancake syrup
 - b. High glycemic foods such as sugar cubes, glucose tablets, or cake icing
 - c. Do not use meal or snack as a hypoglycemic treatment because it may take too long to absorb.

2. Retest blood glucose in 15 minutes to check whether management is effective.
 - a. If blood glucose is increasing, treatment is complete. Glucose will continue to rise over the next 45 minutes.
 - b. If blood glucose is not yet rising, repeat treatment. Continue this cycle until successful.
 - c. Once successful, can introduce a meal or snack and follow plan of care accordingly
3. Patients using insulin or at risk of severe hypoglycemia should have a glucagon rescue device available. Now available as a single-use injectable or nasal spray. Dosing should follow recommendations for individual products.

L. Comorbidity Screening

1. Dilated eye examination
 - a. Yearly, starting at diagnosis for type 2 diabetes
 - b. Yearly, starting 3–5 years after diagnosis and the child has reached 11 years of age or puberty for type 1 diabetes
2. Albuminuria
 - a. Urine albumin/creatinine yearly
 - b. Need two confirmatory specimens if greater than 30 mg/g creatinine
 - i. Starting at diagnosis for type 2 diabetes
 - ii. Starting 5 years after diagnosis and child has reached 11 years of age or puberty for type 1 diabetes
3. Fasting lipid panel
 - a. For type 1 diabetes, start once child has reached 2 years of age and when initial glycemic control has been achieved. If initial low-density lipoprotein cholesterol (LDL) is 100 mg/dL (2.6 mmol/L), subsequent testing should be performed at 9–11 years of age.
 - b. For type 2 diabetes, screen at diagnosis once blood glucose has stabilized.
 - c. If LDL is less than 100 mg/dL, rescreen every 3 years for type 1 diabetes and annually for type 2 diabetes.
 - d. If abnormal, retest annually for type 1 diabetes and every 6 months for type 2 diabetes.
4. Blood pressure measured at every visit
5. Celiac: Immunoglobulin A antitissue transglutaminase at diagnosis for children with type 1 diabetes
6. Hypothyroidism
 - a. Antithyroid peroxidase and antithyroglobulin antibodies at diagnosis in children with type 1 diabetes
 - b. Thyroid-stimulating hormone (TSH) at diagnosis in children with type 1 diabetes once control has begun to stabilize
7. Polycystic ovarian syndrome: Evaluation should be considered in patients with type 2 diabetes if the patient has primary or secondary amenorrhea, hirsutism, and/or significant acne.
8. Non-alcoholic fatty liver disease (NAFLD): Evaluation for NAFLD by measuring alanine aminotransferase and aspartate aminotransferase should be done at diagnosis and annually thereafter in children with type 2 diabetes.
9. Obstructive sleep apnea (OSA): Can screen for OSA in children with type 2 diabetes by asking about snoring, sleep quality, apnea, morning headaches, daytime sleepiness, nocturia, and enuresis
10. Depression: Consider evaluation in children with type 1 diabetes. Evaluate for depression in children with type 2 diabetes at diagnosis and periodically thereafter, particularly in those with frequent emergency department visits or poor glycemic control.
11. Eating disorders: Begin to screen children with type 1 diabetes at 10–12 years of age to help identify disturbed eating behaviors. Diabetes Eating Problems Survey - Revised (DEP-S) is a reliable and brief screening tool for youth. Consider universal screening for patients with type 2 diabetes, especially if patients have poor glycemic control, as part of mental and behavioral health assessment.

12. Neuropathy: For patients with type 1 diabetes, consider yearly foot examinations at start of puberty or when 10 years or older, whichever is earlier, once child has had type 1 diabetes for 5 years. For patients with type 2 diabetes, consider foot examinations at diagnosis and yearly thereafter.
13. Smoking history

II. OBESITY

- A. Diagnosis: Made with BMI calculation applied to Centers for Disease Control and Prevention–derived normative percentiles (Table 3)

Table 3. Diagnostic Criteria

Pediatric BMI	
Underweight	≤5th percentile
Normal	>5th percentile <85th percentile
Overweight	≥85th percentile <95th percentile
Obese	≥95th percentile
Severe obesity	BMI ≥120% of the 95th percentile or an absolute BMI ≥35 kg/m ² , whichever is lower

Patient Case

6. An 11-year-old girl presents with weight 74 kg (above 97%), BMI 33 kg/m² (above 97%), and height 59 inches (at 75%). She tires easily when exercising. She has received no diagnosis of any other disease states. Which would be considered the best initial treatment for her?
 - A. Dietary restriction of 1200 kcal/day.
 - B. Dietary restriction of 850 kcal/day.
 - C. Orlistat.
 - D. Bariatric surgery.

- B. Treatment

1. Intensive lifestyle modification
 - a. Dietary
 - i. Avoid calorie-dense nutrition-poor foods.
 - ii. Control caloric intake through portion control.
 - iii. Reduce dietary saturated fat for children older than 2 years.
 - iv. Increase intake of fiber, fruits, and vegetables.
 - v. 900–1200 kcal/day for 6- to 12-year-olds if greater than 120% ideal body weight: [(Height in cm²) × 1.65]/1000
 - vi. Restrictions of no less than 1200 kcal/day for 13- to 18-year-olds
 - b. Physical activity
 - i. 60 minutes of daily vigorous physical activity
 - ii. Screen time should be limited to 1–2 hours of nonscholastic screen time per day.

- c. Behavioral
 - i. Eat timely, regular meals, including breakfast, while limiting grazing behavior.
 - ii. Behavioral and psychosocial changes should be directed at the entire family.
- 2. Pharmacotherapy is only recommended in children who lack response to intensive lifestyle modification and have severe comorbidities.
 - a. Orlistat
 - i. Gastric and pancreatic lipase inhibitor
 - ii. The only oral FDA-approved weight-loss drug for children 12 years and older
 - (a) 120 mg three times/day with each main meal containing fat
 - (b) Administer during or up to 1 hour after the meal.
 - (c) Modest effect on weight (average of 5% of body weight over 1 year)
 - (d) High occurrence of GI adverse effects
 - b. Metformin
 - i. Does not carry an FDA indication for weight loss in children, but does carry an indication for children 10 years or older with type 2 diabetes
 - ii. Can be used in a manner similar to that in type 2 diabetes treatment. For children at least 10 years of age, the recommended maximal daily dose is 2000 mg
 - c. Glucagon-like peptide 1 agonists
 - i. Liraglutide (Saxenda) received FDA approval for obesity in adolescents in December 2020. Indicated for pediatric patients 12-years-old and older with body weight above 60 kg and initial BMI corresponding to 30 kg/m² or greater for adults (obese) by international cut-offs
 - ii. Initiate at 0.6 mg per day for one week. In weekly intervals, increase the dose until a dose of 3 mg is reached.
- 3. Bariatric surgery may be an option for children with severe comorbidities who have not been successful with life style modifications and pharmacotherapy options. Serious consideration must be given to the risks involved with this option. In addition to the potential risks and complications from surgical procedures in children, the effects on nutritional maintenance, and absorption of nutrients and medications should be considered. Bariatric surgery is recommended only when all the following are met:
 - a. Child is at Tanner stage 4 or 5.
 - b. Child is near final adult height.
 - c. BMI is 40 kg/m² or 35 kg/m² with severe comorbidities.
 - d. Child has no response to a formal program of intense lifestyle modification.
 - e. Child and family pass a psychological examination for stability and competence.
 - f. Child can adhere to diet and activity plan.

III. HYPERTHYROIDISM

- A. Definition: Clinical and biochemical syndrome caused by oversecretion of thyroid hormone
- B. Clinical Presentation
 - 1. Possible thyroid enlargement
 - 2. Photophobia, diplopia, or exophthalmos
 - 3. Nervousness and anxiety
 - 4. Heart palpitations/tachycardia
 - 5. Heat intolerance
 - 6. Weight loss or failure to gain weight with increased appetite
 - 7. Decreased school performance
 - 8. Unusual height increases

9. Easily fatigued or muscle weakness
10. Frequent bowel movement or diarrhea
11. Sleep disturbances
12. Vision changes
13. Menstrual disturbances (decreased flow)

C. Diagnosis

1. High T_4 , high T_3
2. If TSH is low, indicates primary hyperthyroidism
3. If TSH is high, may be pituitary disorder

D. Causes of Hyperthyroidism

1. Graves disease: Most common cause of primary hyperthyroidism
 - a. Autoimmune syndrome
 - b. Thyroid-stimulating antibodies directed at TSH receptors (mimics TSH)
 - c. TSH undetectable because of negative feedback by elevated thyroid hormone concentrations
 - d. Enlarged thyroid gland (goiter), two to three times the normal size
 - e. Commonly develop exophthalmos and pretibial myxedema (eventually)
 - f. Can have spontaneous remission; abnormalities in causative antibody production cease
2. Additional causes of hyperthyroidism
 - a. Toxic adenoma (TSH-secreting pituitary tumor)
 - b. Toxic multinodular goiter (Plummer disease)
 - c. Iodine-induced hyperthyroidism: iodine load following administration of contrast dyes and amiodarone
 - d. Excessive ingestion of thyroid hormone (thyrotoxicosis medicamentosa)

E. Goals of Therapy

1. Eliminate excess thyroid hormone.
2. Minimize symptoms and long-term consequences.

Patient Case

7. A 6-year-old girl presents with Graves disease. Her TSH is low, and her free T_4 is 0.5 times higher than the upper limit of normal. She has been experiencing diarrhea, weight loss, and some vision changes. Which would be considered the best initial treatment for her?
- A. Radioactive iodine (RAI; I-131).
 - B. Methimazole.
 - C. Propylthiouracil.
 - D. Lugol solution.

F. Treatment

1. Individualized therapy based on:
 - a. Type and severity of hyperthyroidism: Treat underlying condition for non-Graves disease.
 - b. Age
 - c. Sex
 - d. Comorbidities
 - e. Goiter size

2. Treatment options
 - a. RAI
 - b. Antithyroid drugs
 - c. Surgical intervention
3. RAI
 - a. I-131 used
 - b. Usually become hypothyroid and require lifelong thyroid replacement
 - c. Secondary therapy for Graves disease; however, may be first-line option for children older than 10 years
 - i. Lifelong thyroid replacement after the use of RAI
 - ii. Concern for increased radiation exposure and risk of cancer
 - iii. Chance of remission when using antithyroid drugs
 - iv. Usually considered only in older children who have not achieved remission, and long-term drug therapy is not desired or has caused complications
 - d. Cardiac patients with Graves disease
 - i. Pretreat with antithyroid.
 - ii. Depletes stored hormone
 - iii. Use of adjunctive antithyroid reduces chances of posttreatment hyperthyroidism
 - e. Contraindicated in pregnancy; requires negative pregnancy test
4. Antithyroid drugs
 - a. Thiourea class (two available in the United States)
 - b. Treatment of choice in most pediatric cases
 - c. Share several mechanisms to inhibit biosynthesis of thyroid hormone. Blocks iodine's ability to combine with tyrosine to form T_4 and triiodothyronine (T_3); also inhibits peripheral conversion of T_4 to T_3
 - d. Both drugs well absorbed in GI tract and actively concentrate in thyroid gland
 - e. Methimazole
 - i. Preferred treatment
 - ii. Available as 5- and 10-mg tablets, which can be halved or quartered
 - iii. Initial: 0.2–0.5 mg/kg/dose once daily. Dose can be increased by 50%–100% and divided if baseline free T_4 is greater than 1.5 times the upper limit of normal
 - iv. Usually takes 4–8 weeks to see full reduction and begin maintenance
 - v. Maintenance: Reduce dose to lowest effective at maintaining euthyroid (usually 50% of initial dose).
 - vi. Therapy should be continued for 1–2 years.
 - vii. Pregnancy warning: Has been associated with birth defects during the first trimester. To avoid these potential congenital defects, propylthiouracil is the treatment of choice when indicated just before or during the first trimester; however, methimazole can be used during the second and third trimesters.
 - f. Propylthiouracil
 - i. No longer recommended for use in children because of high risk of hepatotoxicity
 - ii. Available as 50-mg tablets
 - iii. Initial dose:
 - (a) 6–10 years old: 50 to 150 mg/day divided every 8 hours
 - (b) ≥ 10 years old: 150 to 300 mg/day divided every 8 hours
 - (c) Alternatively: 5–7 mg/kg/day in divided doses every 8 hours
 - iv. Maintenance: One third to two thirds of initial dose

- v. Boxed warnings for hepatotoxicity and pregnancy: The pregnancy warning is not related to propylthiouracil, but directed toward methimazole. Warning indicates that although methimazole is the preferred agent, propylthiouracil may be treatment of choice during or just before first trimester.
- g. Patients considered in remission when they are euthyroid for 1 year with antithyroid medication
- h. Monitoring
 - i. Symptomatic improvement
 - ii. Normalization of laboratory values
 - iii. ADRs: Dose-dependent
 - (a) Benign transient leukopenia (most common)
 - (b) Agranulocytosis (most severe but rare)
 - (c) Pruritic maculopapular rash
 - (d) Arthralgias
 - (e) Fever
 - (f) GI intolerance
 - (g) Hepatotoxicity
- 5. Surgical removal
 - a. Should be considered if:
 - i. Thyroid cancer is present.
 - ii. Patient is unable to achieve remission on antithyroid medication, and long-term drug treatment is not desired or has caused complications.
 - iii. Pregnant patients are intolerant of antithyroid medications.
 - iv. Secondary for children younger than 5 years or third-line therapy for older children whose RAI therapy has failed
 - b. Requires skilled surgeon to avoid complications
 - c. Complications:
 - i. Hypothyroidism (almost 100% for total thyroidectomy)
 - ii. Vocal cord paralysis
 - iii. Hypoparathyroidism
 - iv. Transient hypocalcemia
- 6. Iodide therapy
 - a. Acutely blocks thyroid hormone release (not hormone synthesis)
 - b. Thyroid hormone will begin to leak after 1–2 weeks of treatment.
 - c. Used before thyroidectomy to decrease gland size and vascularity
 - d. Also used after RAI therapy
 - e. Available products:
 - i. Saturated solution potassium iodide: 38 mg per drop
 - ii. Lugol solution: 6.3 mg per drop
 - f. Usual dose: 150–350 mg three times daily in water or juice
 - g. Dosed for 7–14 days before surgery
 - h. ADRs: Rash, drug fever, salivary gland swelling, iodism (toxicity resulting in thirst, diarrhea, weakness, and convulsions), gynecomastia
- 7. β -Blockers
 - a. Used for symptomatic relief
 - i. Palpitations
 - ii. Anxiety, tremor
 - iii. Heat intolerance
 - b. Considered primary therapy in thyroiditis and iodine-induced hyperthyroidism

- c. Propranolol is commonly used.
 - i. 0.5–2 mg/kg/day divided every 8 hours; maximum dose: 40 mg; dosed to symptom relief
 - ii. Metoprolol or atenolol can be substituted if the child has asthma.
- 8. Thyroid storm
 - a. Rare but life-threatening medical emergency
 - b. Precipitating factors:
 - i. Infection
 - ii. Trauma
 - iii. Surgery
 - iv. RAI treatment
 - v. Withdrawal from antithyroid drugs
 - c. Presentation
 - i. High temperature (greater than 39.4°C [103°F])
 - ii. Tachycardia
 - iii. Tachypnea
 - iv. Dehydration
 - v. Delirium, coma
 - vi. Nausea, vomiting, diarrhea
 - d. Limited evidence or guidance for pediatric treatment plan
 - i. High-dose thiourea medication: Suppresses hormone secretion and formation
 - ii. Iodides: Block release of preformed hormone
 - iii. β -Blocker
 - iv. Corticosteroids
 - v. Fluid and electrolyte replacement
 - vi. Antipyretic
 - e. Treat complications or precipitating factors.

IV. HYPOTHYROIDISM

- A. Definition: Clinical and biochemical syndrome caused by under-secretion of thyroid hormone
- B. Clinical Presentation
 - 1. Goiter
 - 2. Dry, coarse skin and hair
 - 3. Cold intolerance
 - 4. Constipation
 - 5. Weight gain (fluid retention)
 - 6. Fatigue, weakness, depression
 - 7. Bradycardia
 - 8. Delayed growth or maturation
 - 9. Forgetfulness, slower thinking, inability to concentrate
- C. Diagnosis
 - 1. Low T_4
 - 2. If TSH high, indicates primary hypothyroidism
 - 3. If TSH low, indicates secondary or central hypothyroidism

D. Higher-Risk Populations

1. Family history of autoimmune thyroid disorders
2. Previous head, neck, or thyroid irradiation or surgery
3. Other autoimmune endocrine and nonendocrine conditions
4. Down and Turner syndromes

E. Causes of Primary Hypothyroidism

1. Autoimmune: Hashimoto disease (most common)
2. Iatrogenic
 - a. Surgical removal of thyroid gland
 - b. Ablation with RAI
3. Lymphoma
4. Drug-induced: lithium or interferon
5. Iodine deficiency
6. Thyroid hypoplasia

F. Goals of Therapy

1. Restore normal thyroid hormone concentrations in tissue.
2. Provide symptomatic relief.
3. Prevent neurologic deficits in newborns and children.
4. Reverse biochemical abnormalities.

Patient Case

8. A 15-year-old male adolescent with type 1 diabetes presents with hypothyroidism. His TSH is high at 8.4 mIU/L, and his free T_4 is 0.25 times lower than the lower limit of normal. He has been experiencing constipation, weight gain, and fatigue. Which would be considered the best initial treatment for him?
- A. Liothyronine.
 - B. Desiccated thyroid.
 - C. Levothyroxine.
 - D. Lugol solution.

G. Treatment of Hypothyroidism

1. Drug of choice is levothyroxine (T_4 ; l-thyroxine)
 - a. Chemically stable
 - b. Relatively inexpensive
 - c. Free of antigenicity
 - d. Uniform potency
 - e. Results in pool of T_4 that is readily and consistently converted to T_3
 - f. Half-life is about 7 days; therefore, once-daily dosing
2. Available in 25- to 300-mcg tablets, capsules, and oral solution (various strengths). There is also a liquid-filled capsule available that has no filler agents. White tablets are available for dye sensitivities.
3. Initial oral dosing (intravenous dosing is completely different and is usually reserved for specific serious situations such as myxedema coma)
 - a. 1–3 months: 10–15 mcg/kg once daily
 - b. 3–6 months: 8–10 mcg/kg once daily
 - c. 6–12 months: 6–8 mcg/kg once daily
 - d. 1–5 years: 5–6 mcg/kg once daily

- e. 6–12 years: 4–5 mcg/kg once daily
- f. Older than 12 years with incomplete growth and puberty: 2–3 mcg/kg once daily
- g. Adolescents with growth and puberty complete: 1.7 mcg/kg once daily
4. Additional dosing concerns
 - a. Therapeutic interchange discouraged because of variability between manufacturers; switching manufacturers should be treated the same as a dose change
 - b. Dose can be titrated weekly in 25% increments to reduce hyperactivity in older children.
 - c. For severe hypothyroidism, consider initiating at 25 mcg/day and adjusting dose more often (every 2–4 weeks).
 - d. If there is concern for cardiac failure, consider lowering the starting dose.
5. Dose and adjustments
 - a. Dependent on symptomatic improvement
 - b. Thyroid function tests
 - i. Thyroid tests should be obtained every 6–8 weeks after dose adjustments and every 3–6 months while the child is still growing.
 - ii. TSH should be in the middle of normal range.
6. Should be taken by itself on empty stomach separated from food or medications by 30–60 minutes (first thing in morning or at bedtime)
 - a. Absorption decreased because of high affinity to bind to other substances
 - b. Patient should be sufficiently educated on administration recommendations and importance of consistency in how it is taken to achieve consistent and positive results.
7. Other options not recommended
 - a. Desiccated thyroid (Thyroid USP)
 - i. Derived from pig, beef, or sheep thyroid gland
 - ii. Armour Thyroid-dosed in grains (1 grain is about equal to 60 mcg of T_4)
 - iii. May be antigenic in allergic or sensitive
 - iv. Variable potency
 - b. Liothyronine (T_3)
 - i. Higher cost
 - ii. Shorter half-life of around 1.5 days
 - iii. Higher incidence of cardiac adverse effects
8. Monitoring
 - a. Symptomatic improvement
 - i. Some in first week
 - ii. Maximal effect may take weeks.
 - b. Assess for ADRs associated with preparation used.
 - i. ADRs from all preparations can be similar to those associated with hyperthyroidism (e.g., tachycardia, heat intolerance, weight loss, diarrhea, anxiety, irritability).
 - ii. For desiccated thyroid and thyroglobulin, should also monitor for hypersensitivity
 - iii. For liothyronine, monitor for more severe cardiovascular effects such as arrhythmia and hypotension.
 - c. Too much thyroid replacement is possible.
 - i. Check for common signs and symptoms of hyperthyroidism.
 - ii. Cardiac abnormalities (tachycardia, angina, heart failure)
9. Congenital hypothyroidism
 - a. Caused by improper development of thyroid or thyroid hormone synthesis
 - b. Levothyroxine 10–15 mcg/kg/day should be initiated immediately.
 - c. Universal newborn screening is recommended. Laboratory tests should be done at 2–4 days of age

H. Myxedema Coma

1. Long-standing, uncorrected hypothyroidism
2. Life-threatening event
3. Hypothermia, extreme hypothyroid symptoms plus coma or delirium
4. Treatment
 - a. Intravenous levothyroxine 200–400 mcg once
 - b. Delay enteral therapy because of decreased bioavailability of oral T₄.

V. SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE**A. Definition: Water intake exceeds the kidney's capacity to excrete.**

1. Increased vasopressin (antidiuretic hormone [ADH]) release
2. Enhanced sensitivity of the kidney to ADH

B. Presentation

1. Patients are hyponatremic (sodium less than 130 mEq/L).
2. Urine osmolality is generally greater than 100 mOsm/kg (100 mmol/kg).
3. Urine sodium concentration is usually greater than 25 mEq/L (25 mmol/L).

C. Causes

1. Malignancies such as lung carcinoma, lymphoma, Ewing sarcoma, and central nervous system tumors
2. Central nervous system disorders (e.g., head trauma, stroke, meningitis, pituitary surgery)
3. Pulmonary disease (e.g., tuberculosis, pneumonia, acute respiratory distress syndrome)
4. Medications (e.g., nicotine, opioids, certain antiepileptics, certain antidepressants, certain chemotherapy agents)

D. Treatment

1. Treatment goal: Correct sodium and water imbalances.
2. Resolve underlying cause, and remove offending medications.
3. Water restriction (1000 mL/m²/day); may be challenging in small children because of caloric demand relative to water intake
4. 0.9% NaCl (sodium chloride) solution plus a loop diuretic can be used if water restriction is inappropriate or inadequate.
 - a. Furosemide oral: 2 mg/kg once daily or divided for twice-daily administration
 - b. Furosemide intravenous: 1–2 mg/kg/dose every 6–12 hours
5. In children older than 8 years, demeclocycline can be used.
 - a. Vasopressin receptor antagonist
 - b. Oral: 8–12 mg/kg/day divided every 6–12 hours
 - c. In children younger than 8 years, it can interfere with tooth and bone development.
6. Demeclocycline should not be used in patients with liver disease.
 - a. Common ADRs: Photosensitivity, rash
 - b. Serious ADRs: DI, Stevens-Johnson syndrome, angioedema
 - c. Monitor sodium and urine output
7. Urea and vaptans (i.e., tolvaptan, conivaptan) currently have limited pediatric data but are FDA approved for adults with chronic SIADH

VI. ADRENAL INSUFFICIENCY

- A. Primary Adrenal Insufficiency, Primarily Addison Disease or Congenital Adrenal Hyperplasia in Children: Damage to adrenal cortex causes deficiencies primarily in cortisol and aldosterone
- B. Symptoms
 1. General adrenal insufficiency: weakness, GI symptoms, craving for salt, headaches, confusion, failure to thrive, depression, and postural dizziness
 2. Symptoms more specific to Addison disease: weight loss, dehydration, hyponatremia, hyperkalemia, and elevated blood urea nitrogen
 3. Diagnosis should be made using intravenous corticotropin stimulation test. If not feasible, a morning cortisol level less than 5 mcg/dL may be used in combination with ACTH.
- C. Treatment
 1. Treatment of primary insufficiency centers on replacement of both glucocorticoids and mineralocorticoids.
 2. Glucocorticoid loss: Preferred treatment is hydrocortisone 7–12 mg/m²/day given orally in three divided doses.
 - a. Preferred because of its low potency and shorter half-life
 - b. Doses can be divided unequally, with higher amounts in the morning than in the evening to better mimic normal release.
 - c. Oral tablets available in 5 mg, 10 mg, and 20 mg strengths. Oral capsule sprinkles available at smaller strengths of 0.5 mg, 1 mg, 2 mg, and 5 mg to accommodate younger/smaller patients.
 - d. Prednisone, dexamethasone, or other systemic steroids can be used at cortisol-equivalent doses; however this is not preferred because of differing anti-inflammatory and growth suppressive effects.
 3. Mineralocorticoid loss: Preferred treatment is fludrocortisone 0.05–0.2 mg once daily. Consider the need for NaCl supplementation for the first 6–12 months of age (1–2 g/day).
 4. Monitor for clinically relevant effects such as appropriate growth, weight gain, and reduction of symptoms.
 5. Adverse effects: gastric upset, hypertension, hyperglycemia, hypokalemia, insomnia, excitability, and edema
- D. During periods of stress, glucocorticoid doses may need to be doubled. Major stress may require even larger increases.
- E. Patients should carry medical identification and have access to emergency doses of glucocorticoid (injectable or suppository).
- F. Secondary insufficiency should be treated by addressing the underlying cause in addition to short-term glucocorticoid management.

VII. DIABETES INSIPIDUS

- A. Definition: Inability to concentrate urine, resulting in polyuria and polydipsia
- B. Classification:
 1. Central DI caused by decreased ADH
 2. Nephrogenic DI caused by decreased kidney response to ADH

C. Presentation

1. Patients with central DI often present with sudden onset of polyuria, whereas patients with nephrogenic DI develop polyuria more gradually.
2. Symptoms: Onset is more sudden with central DI.
 - a. Poor feeding
 - b. Failure to thrive
 - c. Irritability
 - d. Fever of unknown origin
 - e. Constipation
 - f. Excessively wet diapers
 - g. Extreme thirst
 - h. Polyuria

D. Causes

1. Central: head trauma, neurosurgery, tumors, hereditary
2. Nephrogenic: hypercalcemia, hypokalemia, renal disease, hereditary, drug induced.
3. Medications: lithium, amphotericin B, demeclocycline, chemotherapy agents (e.g., vinblastine, cisplatin, cyclophosphamide, ifosfamide), cidofovir and other HIV (human immunodeficiency virus) medications

E. Complications

1. Developmental delay
2. Growth retardation
3. Seizures

F. Diagnosis

1. A water deprivation test can confirm diagnosis and differentiate type.
 - a. Obtain baseline urine and blood laboratory values, including serum electrolytes.
 - b. Deprive patient of water until dehydration occurs (total of 2%–5% weight loss, measured every hour), a maximum of 4 hours for infants and 7 hours for children.
 - c. Measure urine and blood osmolality before and after administering desmopressin.
 - i. Central DI: Prompt increase in urine osmolality to greater than 450 mOsm/kg
 - ii. Nephrogenic DI: Urine osmolality will remain less than 200 mOsm/kg.
2. In patients with hypernatremia, a plasma ADH concentration and response to desmopressin can be obtained and evaluated without water deprivation.

G. Treatment

1. Central DI
 - a. Desmopressin is first-line therapy.
 - b. Oral tablets are usually preferred.
 - i. Available in 0.1- and 0.2-mg tablets and can be split
 - ii. Children 12 years and younger: initially 0.05 mg twice daily titrate to response
 - iii. Children older than 12 years: 0.05 mg twice daily

- c. Intranasal formulation may be a consideration if oral administration is challenging or if there is variability with absorption of oral formulation.
 - i. Use caution when selecting an intranasal product because of differences in delivered dose and mode of administration.
 - (a) Intranasal spray:
 - (1) Minimum dose deliverable is 10 mcg.
 - (2) Use in patients with doses of 10 mcg or greater.
 - (b) Intranasal solution:
 - (1) Administered by nasal tube supplied by manufacturer
 - (2) Deliverable as 0.025 mL/squirt with 10 mcg/0.1 mL (2.5 mcg/squirt)
 - (3) Use in patients with doses less than 10 mcg.
 - ii. Children 3 months to 12 years or younger: initial dose of 5 mcg/day intranasal divided
 - iii. Children older than 12 years: initial dose of 5 to 40 mcg/day intranasal divided, typically 20 mcg/day
 - d. Sublingual formulation is currently only FDA approved for adults but has been studied in children and is approved for pediatric use in other countries. Initial dose: 60 mcg three times daily
 - e. Morning and evening doses should be adjusted separately for an adequate diurnal rhythm of water turnover.
 - f. Caution should be used when switching formulations, because equivalent dosages represent 10- to 20-fold differences in dose.
 - g. Monitor for tachyphylaxis.
 - h. Because of high relative fluid intake in neonates and young infants, consider fluid treatment alone with possible addition of chlorothiazide.
 - i. Avoids risk of hyponatremia when desmopressin used
 - ii. Chlorothiazide: 10 mg/kg/day orally in two divided doses
2. Nephrogenic DI
- a. Desmopressin will not work because the kidney is resistant to it.
 - b. Treat underlying problem, if applicable.
 - c. Ensure the intake of adequate calories for growth.
 - d. Avoid severe dehydration.
 - e. Sodium restriction
 - f. Thiazide diuretics in combination with amiloride or indomethacin
 - i. Thiazide and amiloride are preferred.
 - ii. Thiazide and amiloride are better tolerated in children.
 - iii. Amiloride counteracts thiazide-induced hypokalemia.
 - iv. Indomethacin carries risk of nephrotoxicity.
 - g. Hydrochlorothiazide: 2–3 mg/kg/day
 - h. Chlorothiazide: 10 mg/kg/day orally in two divided doses
 - i. Amiloride:
 - i. Children 6–20 kg: 0.625 mg/kg/day in one or two divided doses; maximum dose: 10 mg/day
 - ii. Children weighing more than 20 kg and adults: 5–10 mg/day in one or two divided doses; maximum dose: 20 mg/day

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Additional Medication Dosing

1. Lexi-Comp Online [Internet database]. Hudson, OH: Lexi-Comp. Updated periodically.

ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Using 0.5 unit/kg, the TDD is 30 units. For NPH, using the two-thirds morning and one-third evening method would yield 13 units of NPH and 7 units of short acting in the morning plus 7 units of NPH and 3 units of short acting in the evening (Answer C is correct). Although Answer A has an appropriate evening dose, the morning dose is reversed. Answer B does not divide the doses appropriately. Answer D uses a starting dose of 1 unit/kg, which may be too aggressive.

2. Answer: B

Using 0.5 unit/kg, the TDD is 30 units. For this type of regimen, the basal dose is usually about 50% of TDD, which is 15 units (Answer B). Answer A would be 50% of a TDD that is less than 0.3 unit/kg, or only about 25% of an appropriate TDD. Either way, it would not provide the best chance of lowering blood glucose to an appropriate concentration. Answers C and D both overestimate the patient's basal needs and would probably result in hypoglycemic periods.

3. Answer: B

Using 0.5 unit/kg, the TDD is 30 units. One of the most common methods to calculate an I:CHO is the 500 method: $500/\text{TDD} = \text{around } 16$. Answer B comes closest to this number. Answer A is twice as aggressive and might be calculated if 1 unit/kg were used for the TDD. Answers C and D are much smaller doses and might be calculated if using a TDD of 0.25 unit/kg or less. They also might be achieved if using the formula for ISF instead of I:CHO.

4. Answer A

Using 0.5 unit/kg, the TDD is 30 units. One of the most common methods of calculating an ISF is the 1800 method: $1800/\text{TDD} = 60$ (Answer A). Answer B is twice as aggressive and might be calculated if 1 unit/kg were used for the TDD. Answers C and D are much larger doses and might be calculated if using a TDD of 2 units/kg or more. They also might be achieved if using the formula for I:CHO instead of ISF.

5. Answer: D

This patient's problem areas are right before dinner (evening fasting) and right before bedtime (fasting). In an NPH regimen, the morning NPH is responsible

for lowering blood glucose concentrations after lunch. The dinner short acting is responsible for lowering concentrations after dinner. Therefore, an increase of about 20% in these two doses best addresses this case (Answer D). Answer A addresses post-breakfast and post-lunch blood glucose concentrations. Answer B addresses post-dinner and overnight control. Answer C addresses post-breakfast and post-dinner and the move to a three-injection regimen.

6. Answer: A

For children 6–12 years of age, diet restriction can be used as part of lifestyle modifications if the child is significantly above the ideal weight. The recommended range is 900–1200 kcal (Answer A). Answer B is too aggressive. Oral medications and bariatric surgery should be reserved for more serious situations in which lifestyle modification has failed and the patient has severe comorbidities; therefore, Answers C and D are not the best options.

7. Answer: B

For primary hyperthyroidism in children, antithyroid drugs are considered first line to determine whether remission can be achieved without causing permanent hypothyroidism. Methimazole is the preferred agent because of its better safety profile and once-daily dosing (Answer B). Answer A is an option for treatment and is first line in adults. However, because of safety concerns in children, it is reserved for older children with lack of response to antithyroid medications. Answer C is a valid option because it is an antithyroid medication; however, it is not preferred to methimazole because of its adverse effect profile, including hepatotoxicity, and thrice-daily dosing. Answer D is used for short-term treatment usually before or after radiation or surgery; therefore, it is not the best option.

8. Answer: C

The treatment of choice for hypothyroidism is levothyroxine (Answer C). Although Answers A and B are also replacement therapies, they are not preferred in children. Answer A, liothyronine, replaces T_3 only, so it has a much shorter half-life. It is also very expensive and has an increased adverse effect profile with no demonstrated benefits. Answer B, desiccated thyroid, has a large degree of variability from dose to dose and

carries the possibility of antigenicity. Answer D, Lugol solution, is used for short-term treatment of hyperthyroidism, usually before or after radiation or surgery; therefore, this is not an option.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

The patient is an 11-year-old girl (weight 30 kg) with newly diagnosed type 1 diabetes who requires insulin. Insulin glargine 7.5 units subcutaneously once daily in the morning and insulin aspart 2.5 units 15 minutes before each meal would be the most appropriate regimen, making Answer D correct. This combination of a long-acting basal insulin and a rapid-acting bolus insulin is appropriately dosed according to the patient's weight (15 units daily = about 0.5 unit/kg/day). Although Answer A also uses the glargine/rapid-acting regimen, its dose is twice that of the correct answer, making Answer A incorrect. The basal insulin regimen in Answer D is dosed once daily compared with the low-dose insulin detemir represented in Answer C, which should be dosed twice daily and, compared with the NPH dosing in Answer B, is associated with less hypoglycemia, making Answers B and C incorrect.

2. Answer: B

The most appropriate intervention would be to increase metformin to 1000 mg twice daily (Answer B), making this the correct answer. The A1C concentration is not at the target value, but the patient is not at the maximal daily metformin dosage (2000 mg daily in children 10 years or older). It would be more appropriate to maximize metformin monotherapy than to add another drug. Metformin is the initial therapy recommended by the ADA for adolescents. In addition, metformin is the only oral noninsulin diabetes mellitus drug labeled for use in children and adolescents. Although the lack of a labeled indication is not always a reason not to use a medication, especially in pediatric patients, metformin has more literature supporting its use and superior efficacy than the agents in Answers A and C. Moreover, given the patient's mild degree of hyperglycemia, adding insulin is unwarranted (Answer D), and a basal insulin would most likely be the choice when it is warranted.

3. Answer: B

The patient has high blood glucose concentrations on waking. The medication responsible for this period (overnight) is glargine. The patient also has high glucose concentrations before lunch. Moreover, these are higher than the morning high concentrations. Thus, changing glargine alone will not be sufficient. The

breakfast fast-acting insulin should be keeping this down. A 10%–20% increase in these two doses is the correct answer (Answer B). Answer A addresses only the lunchtime high readings, and Answer C answers only the overnight problem. Answer D is overly aggressive and increases coverage of dinner and bedtime readings, which were already well controlled; thus, using this option could cause hypoglycemia.

4. Answer: A

Answer A, desmopressin, is the first-line therapy for DI. It is typically dosed at 0.05 mg twice daily for children younger than 12 years. Answer C is incorrect because, although polyuria is an issue, the cause is not a build-up of extra fluid but an inappropriate release of fluid; therefore, water restriction could lead to dehydration. Similarly, Answer B is incorrect; although steroids might affect water retention, they do not address the underlying problem, and central DI is not associated with steroid imbalances. Answer D is a synthetic cofactor BH_4 (tetrahydrobiopterin) and would have no effect on this disease.

5. Answer: C

For SIADH, water restriction (Answer C) is first-line therapy. This is usually limited to no more than 1000 mL/ m^2 /day. Answers A and B are not the best choices because the problem is with fluid retention, and these would make it worse. Answer D is a diuretic and would facilitate water removal, but it is usually instituted after water restriction has failed.

6. Answer: B

In adrenal insufficiency, replacement of steroids is paramount. The combination of hydrocortisone and fludrocortisone (Answer B) ensures both glucocorticoid and mineral corticoid replacement. Although dehydration is a problem, the use of Answers A and C to retain fluid is not recommended, nor do they address the underlying problem. Answer D is a synthetic cofactor BH_4 (tetrahydrobiopterin) and would have no effect on this disease.

7. Answer: C

Hashimoto disease is primary hypothyroidism, for which the treatment of choice is levothyroxine at 4–5 mcg/kg/day (Answer C). Although Answer B,

liothyronine, replaces T_3 , it is expensive, has a shorter half-life, and has an increased adverse effect profile. Answer A, methimazole, and Answer D, iodide, are antithyroid drugs that do not address the underlying problem.

8. Answer: A

For primary hyperthyroidism in children, antithyroid drugs are considered first line to check whether remission can be achieved without causing permanent hypothyroidism. Answer A, methimazole, is the preferred agent because of its better safety profile and once-daily dosing. Answers B and C are thyroid replacement therapies and are used in Graves disease only after permanent hypothyroidism has been induced by radiation or surgery. Answer D is used for short-term treatment, usually before or after radiation or surgery; therefore, it is not the best option.

9. Answer: B

Pharmacotherapy should be used only in certain circumstances, and this child meets these criteria. Answer B, orlistat, is the only agent approved for children 12 years and older and has a good safety profile. Answer A, phentermine, and Answer C, sibutramine, although used in weight loss, do not have a pediatric indication, and they have more potential adverse effects. Answer D, bariatric surgery, is not the best option in this situation because it has even more restrictive criteria for use in children, which are not met in this case.

10. Answer: D

The patient is experiencing a mild hypoglycemic event. The most appropriate treatment is to follow the “rule of 15,” which means the patient should take a controlled amount of glucose to increase his blood glucose in a controlled way (Answer D). This treatment should be separate from any meal or insulin dose. Answer A (take 1 unit of aspart insulin because the ISF is 1:50) would facilitate the continuation of the hypoglycemic event. Answer B (do nothing until the next scheduled meal and injection time) is not the most appropriate choice; it could be dangerous not to treat the patient’s low blood glucose immediately, because it could worsen. Although Answer C uses a fast-acting sugar to raise blood glucose concentrations, its effects are essentially negated by giving insulin for it.

11. Answer: D

The fasting goal for those 13–19 years of age is 90–130 mg/dL. The bedtime goal is 90–150 mg/dL (Answer D is correct; Answers B and C are incorrect). Answer A, less than 180 mg/dL, is a postprandial range.

12. Answer: D

Answer D, amiloride, is the preferred medication to be used with thiazide diuretics because of its safety profile and potassium-sparing effect. Answer B, indomethacin, could be used, but it has more safety concerns. Answer A, desmopressin, is not effective in nephrogenic DI because of the kidneys’ resistance to it. The slow onset of symptoms and failure of the water deprivation test suggest nephrogenic DI. Chlorothiazide (Answer C) could be used as therapy, but because the patient is already taking a thiazide, this would not be a good additive option.

PHARMACOKINETICS, PHARMACODYNAMICS, PHARMACOGENOMICS AND DRUG FORMULATIONS

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Learning Objectives

1. Understand the effect of maturational development from a neonate to an adult on drug absorption after administration by different routes.
2. Compare the differences in distribution of hydrophilic and lipophilic drugs in the pediatric population as the newborn matures into an adolescent and an adult.
3. Explain the impact of maturational changes from a neonate to an adult on drug-metabolizing enzymes involved in phase I and phase II reactions.
4. Recognize the effect of physical and physiologic development on renal function, and make dosing recommendations for renally eliminated drugs using various noninvasive methods of estimating renal function.
5. Explore the differences between adults and children in how drugs can affect the body (pharmacodynamics).
6. List key pharmacogenomic variations that may affect efficacy, safety, and dosing of drugs in children.
7. Describe the need for, the methods of, and the challenges in compounding extemporaneous formulations in pediatric patients.

Abbreviations in This Chapter

ABW	Actual body weight
BSA	Body surface area
GA	Gestational age
IBW	Ideal body weight
NUDT15	Nucleotide diphosphatase enzyme
PD	Pharmacodynamics
PNA	Postnatal age
TDM	Therapeutic drug monitoring
TPMT	Thiopurine S-methyltransferase
UGT1A1	Uridine 5'-diphosphate glucuronosyltransferase 1A1
USP	United States Pharmacopeia
Vd	Volume of distribution

Self-Assessment Questions

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

1. You are caring for a 30-week gestational age (GA), 21 days postnatal age (PNA) newborn who was slowly transitioned to continuous enteral feeds with preterm infant formula by a nasogastric tube. She has been receiving medication A intravenously, which is absorbed well on an empty stomach when administered enterally. She is transitioned to the liquid formulation through her nasogastric tube. Which would be the most likely cause of decreased absorption of medication A?
 - A. Increased gastric acid production.
 - B. Continuous enteral feeds.
 - C. Decreased gastric emptying time.
 - D. Decreased intestinal emptying time.

Questions 2 and 3 pertain to the following case.

O.H. is 22-week, 3-day GA of PNA 36 days (length 31.5 cm, weight 0.77 kg). E.M. is an 8-year-old (height 118 cm, weight 25 kg).

2. Which is most likely the rationale for differences in transdermal absorption of drugs between O.H. and E.M.?
 - A. E.M. would have increased transdermal absorption relative to her body weight compared with O.H. because of her higher body surface area (BSA)/weight ratio.
 - B. O.H. would have increased transdermal absorption relative to his body weight compared with E.M. because of his higher BSA/weight ratio.
 - C. E.M. would have increased transdermal absorption compared with O.H. because of her thinner epidermis and stratum corneum.
 - D. O.H. would have increased transdermal absorption compared with E.M. because of his mature epidermis and stratum corneum.
3. Which best describes differences in body composition between O.H. and E.M.?
 - A. Lower albumin and α_1 -acid glycoprotein concentrations in O.H. may lead to larger volume of distribution (Vd) for drugs with high protein-binding ability compared with E.M.

- B. Lower total body water content in O.H. compared with E.M. may lead to larger Vd for hydrophilic drugs.
- C. A greater portion of total body water in E.M. is extracellular compared with O.H.
- D. Higher body fat in E.M. may require higher loading doses for lipophilic drugs compared with O.H.
4. A.E. is a 14-year-old male adolescent (height 150.2 cm, weight 76.1 kg) admitted with a central venous access device (CVAD, central line) infection. He is 10 days post chemotherapy for acute myelogenous leukemia, is febrile, and has neutropenia. All of his systems and laboratory values are within normal limits. The preliminary gram stain on blood culture obtained through the CVAD is positive for gram-negative rods. According to institutional clinical practice guidelines, he is initiated on cefepime 50 mg/kg/dose intravenously every 8 hours and gentamicin 7 mg/kg/dose intravenously every 24 hours. Which would be most appropriate for his gentamicin therapy?
- A. Initiate gentamicin 260 mg intravenously every 24 hours. Measure two serum concentrations after the third dose with the goal of optimizing the dose.
- B. Initiate gentamicin 371 mg intravenously every 24 hours. Measure two serum concentrations after the third dose with the goal of optimizing the dose.
- C. Initiate gentamicin 371 mg intravenously every 24 hours. Measure two serum concentrations after the first dose with the goal of optimizing the dose.
- D. Initiate gentamicin 532 mg intravenously every 24 hours. Measure a trough concentration after the third dose to achieve safe trough concentrations.
5. Which best describes maturational changes in phase I drug-metabolizing enzymes?
- A. Higher per kilogram of body weight dosing may be required in a 3-year-old compared with an adult for a drug extensively metabolized by CYP2C9.
- B. Clearance of a drug extensively metabolized by CYP2C19 is fastest in a 32-week GA, 14-day-old newborn.
- C. Half-life of a drug extensively metabolized by CYP3A4 is longest in a 2-year-old child.
- D. Elimination rate constant of a drug extensively metabolized by CYP3A5 is lower in a neonate than in an adult.
6. J.D. is a 6-year-old child (height 119 cm, weight 25 kg) admitted for severe vomiting, lack of oral intake for 24 hours, and dehydration. Abdominal radiography reveals pneumatosis intestinalis. He is initiated on piperacillin/tazobactam 1875 mg intravenously every 6 hours. Among his abnormal laboratory values are SCr 1.3 mg/dL and BUN 30 mg/dL. Prescribing information for piperacillin/tazobactam recommends the following dose adjustments for renal function:
- Glomerular filtration rate (GFR) greater than 50 mL/minute/1.73 m²: No dose adjustments
- GFR 30–50 mL/minute/1.73 m²: 35–50 piperacillin mg/kg/dose every 6 hours
- GFR less than 30 mL/minute/1.73 m²: 35–50 piperacillin mg/kg/dose every 8 hours
- Which is the most appropriate decision as you verify the order?
- A. No dose adjustments are required.
- B. Recommend changing the dose to 1250 mg intravenously every 6 hours.
- C. Recommend changing the dose to 1875 mg intravenously every 8 hours.
- D. Recommend changing the dose to 875 mg intravenously every 8 hours.
7. Which is the most accurate combination of drug and altered pharmacodynamic drug response in the pediatric population and the necessary action?
- A. Ciprofloxacin eardrops in a 1-year-old infant are prohibited because of the risk of damage to the cartilage of weight-bearing joints.
- B. Ceftriaxone for treatment of meningitis should be used with extreme caution in a 3-year-old because of the risk of kernicterus and encephalopathy.

- C. Promethazine as an antiemetic is contraindicated in a 9-month-old because of the risk of severe respiratory depression.
 - D. Doxycycline is contraindicated in the treatment of Lyme disease in a 5-year-old because of the risk of dental staining and darkening of permanent teeth.
8. Which best describes the combination of the drug, the pharmacogenomic influence on its efficacy or safety, and the biomarker that can be tested to mitigate the influence?
- A. Abacavir is contraindicated in patients carrying the *HLA-B*5701* allele to avoid the risk of anaphylaxis and multiorgan failure.
 - B. Patients of Asian ancestry with the *HLA-A*1502* allele are poor metabolizers of phenytoin and should be initiated at the lower end of the dosing range.
 - C. A dose reduction of 10% or less of the standard mercaptopurine dose should be considered in a patient who is heterozygous to both thiopurine S-methyltransferase (TPMT) and nucleotide diphosphatase enzyme (NUDT15) enzymes.
 - D. Use of codeine is contraindicated in CYP2D6 ultra-metabolizers because of the risk of inadequate pain control.
9. The parents of your 3-year-old transplant recipient want to transfer all of their child's prescriptions to a close-to-home pharmacy. This includes compounded tacrolimus oral suspension with a prior authorization. Two formulations have published stability data. The formulations are in 0.5-mg/mL and 1-mg/mL strengths stable at room temperature for 56 days and 120 days, respectively. Which would be your most likely concern regarding transferring such a prescription to another pharmacy?
- A. Lack of bioavailability and efficacy studies.
 - B. Inability to directly extrapolate the expiration date of the commercially available capsules used to compound the suspension to the suspension's beyond-use date.
 - C. Reimbursement for compounding and dispensing the formulation.
 - D. Potential for serious medication error because of lack of standardized concentration being compounded by different pharmacies.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.5
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.1
3. Domain 4: Public Health and Patient Advocacy; Task(s): 4.2

I. INTRODUCTION

- A. Progression of physiologic growth and maturation over time is described using different terminologies (Table 1; Table 2). Duration of normal human gestation is 40 weeks. Date of conception can accurately be determined when conception is achieved using assisted reproductive technology. In these cases, the gestational age (GA) is usually 2 weeks longer than the conceptional age.

Table 1. Selected Birth Age Terminology

Terminology	Birth Age
Gestational age (GA)	Time from first day of last normal menstrual period to birth (in completed weeks)
Conceptional age	Time elapsed between the day of conception and the day of delivery (more applicable and accurate in pregnancies resulting from assisted reproductive technologies)
Postnatal age (PNA) or chronological age	Time elapsed since birth (days, weeks, months, or years)
Postmenstrual age (PMA)	GA + chronological age (weeks)
Corrected age	Chronological age reduced by the number of weeks born before 40 wk of gestation (weeks or months) Reported up to 3 yr of age in children born prematurely

Table 2. Classification of Distinct Pediatric Age Groups

Terminology	Age Grouping
Neonates	Birth to 4 wk of age
Premature neonate	GA < 37 wk at birth
Low birth weight (LBW)	Birth weight < 2500 g (GA < 35 wk)
Very low birth weight (VLBW)	Birth weight < 1500 g (GA < 30 wk)
Extremely low birth weight	Birth weight < 1000 g (GA < 27 wk)
Full-term neonate	GA 39–40 wk at birth
Postterm neonate	GA ≥ 38 wk at birth
Infant	1 to < 12 mo of age
Child	1–12 yr of age
Adolescent	13–18 yr of age
Pediatric	Birth to 18 yr of age

GA = gestational age.

- B. As children grow and cross the threshold into puberty, significant hormonal changes with subsequent changes in lean body mass, body fat content, and total body water occur. In addition, secondary sexual characteristics develop that are assigned to stages using the Tanner scale. However, the effects of these changes on drug disposition are not well described.

II. PHARMACOKINETICS

A. Definition: Pharmacokinetics considers what the body does to the drug.

B. Absorption

1. Oral: Drugs administered by the oral route are mainly absorbed by passive diffusion. The rate and extent of GI absorption depend on several factors such as gastric pH, gastric and intestinal motility, pancreatic enzyme activity, bile salt production, bacterial colonization of the intestines, intestinal drug transporters, blood flow to the GI tract, and surface area of absorption. These undergo considerable maturational changes as a neonate grows into an adult.
 - a. Gastric pH:
 - i. Newborns less than 32 weeks' GA rarely have any gastric acid production.
 - ii. The gastric pH in a newborn at term is alkaline (pH 6–8) but becomes acidic over the next 24 hours (pH 1.5–3).
 - iii. The volume and acid concentration of the gastric fluid approach the lower limit of normal adult values by 3 months of age and reach adult values only after 2 years of age.
 - iv. Gastric/intestinal pH can affect the absorption of drugs that are weak acids or bases depending on their partition coefficient (pKa).
 - v. Acid-labile drugs such as penicillin G have greater bioavailability in neonates than in children and adults. However, weak organic acids such as phenobarbital have decreased bioavailability.
 - vi. Presence of food increases gastric pH to 6–6.5, and pH remains elevated for 1–3 hours after feeding. Infants fed every 2–3 hours or those receiving continuous feeds may have a short to no period where the pH remains acidic. This may significantly affect the absorption of drugs depending on acidic gastric pH. For example, voriconazole should be administered 1 hour before or 1 hour after a child is fed. Continuous enteral tube feeds should be held 1 hour before and 1 hour after oral voriconazole administration.
 - b. GI emptying:
 - i. GI emptying rate or GI transit time is delayed in newborns and infants, reaching adult values by 6–8 months of age.
 - ii. Rate and extent of drug absorption may significantly change depending on their primary site of absorption.
 - iii. Drugs primarily absorbed in the stomach will have a higher rate and extent of absorption with a delayed gastric emptying time.
 - iv. Drugs primarily absorbed in the small intestines will have a lower rate of absorption because of delayed gastric emptying but increased bioavailability (extent of absorption) because of delayed intestinal emptying time.
 - v. GI transit time is also influenced by the presence and type of food. Infant formula takes twice the time to transit through the stomach (gastric emptying) compared with human milk (78 vs. 48 minutes) in term infants. Such a correlation is not evident in preterm infants (GA less than 37 weeks). Calorically dense food, food containing casein or nonhydrolyzed/partially hydrolyzed protein, and long-chain fatty acids may delay gastric emptying time.
 - vi. Intestinal transit time in a preterm newborn is 4 times slower than in an adult but achieves adult values in the rest of the healthy pediatric population.
 - vii. GI transit time can affect drug absorption depending on the type of dosage form (liquid vs. solid vs. extended release). Liquids may have shorter transit time than solid dosage forms.
 - viii. Disorders such as constipation, diarrhea, and short bowel syndrome may significantly affect GI transit time, especially intestinal transit time.

- c. Pancreatic enzymes:
 - i. Pancreatic enzyme activity is low at birth.
 - ii. Amylase activity remains about 10% of adult values even after the first month of life.
 - iii. Lipase activity is present by 34–36 weeks' GA. It increases 5-fold during the first 7 days of life to 20-fold during the first 9 months after birth, remaining lower than in adults.
 - iv. Trypsin secretion is decreased at birth but develops during the first year of life.
 - v. Drug dosing recommendations are not influenced by maturational changes in pancreatic enzyme activity beyond infancy.
 - vi. Bioavailability of oral liquid ester formulations of clindamycin and chloramphenicol palmitate depends on pancreatic enzyme activity needed for intraluminal hydrolysis in the GI tract and absorption.
- d. Bile salts:
 - i. Within the first few months of life, bile salts develop, and maturation continues during the first year of life.
 - ii. Bile salts may influence the absorption of certain fat-soluble drugs (fat-soluble vitamins) and nutrients (dietary lipids). In a concentration-dependent manner, bile salts may extract membrane lipids to form micelles and enhance transcellular transport.
- e. Bacterial colonization
 - i. The effect of the GI microbiome on intestinal motility and drug metabolism in pediatric patients is not completely known.
 - ii. In utero, the infant gut is considered sterile and is colonized during birth and postnatally.
 - iii. The GI bacterial flora approaches adult composition by 4 years of age.
 - iv. Within the pediatric population, there is significant diversity in the microbiome repertoire depending on the birth modes, diet (breast milk or infant formula), GA at birth (preterm or term), and exposure to antibiotics during early life.
 - v. Intestinal colonization in children younger than 2 years by oral digoxin-reducing (inactivating) anaerobic bacteria is less than in adults. This may lead to higher digoxin bioavailability in this age group. The reduction (inactivation) in digoxin by these bacteria observed in adults may not be achieved until adolescence.
- f. Drug transporters
 - i. Information on maturational changes in intestinal drug transporters in pediatric patients is limited and available for multidrug resistance 1 (MDR1), P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance-associated protein 1, multidrug resistance-associated protein 2, and organic anion transporting polypeptide 2B1 (OATP2B1).
 - ii. MDR1/P-gp, multidrug resistance-associated protein 1, multidrug resistance-associated protein 2, and BCRP are efflux transporters present abundantly at the apical (luminal) membrane of the enterocytes, limiting the intestinal absorption of drugs such as cyclosporine, tacrolimus, chemotherapy agents (doxorubicin, daunorubicin, methotrexate), digoxin, imatinib, statins, and fluoroquinolones. OATP2B1 also present at the apical (luminal) membrane of the enterocytes transports sodium-independent organic compounds with high molecular weight and plays a role in the intestinal absorption of drugs such as statins, glyburide, and mesalazine.
 - iii. None of these transporters has a uniform maturational pattern.
 - iv. P-gp and multidrug resistance-associated protein 2 expressions are undetectable in the first trimester of pregnancy and approach adult values at or shortly after birth.
 - v. OATP2B1 expression is higher in neonates and decreases during the first few months of life into adulthood.

2. Rectal: The rectal route of administration is a useful alternative when use of the oral, intravenous, or intramuscular route of administration is not possible (e.g., nausea, vomiting, seizures, preparation for surgery, lack of injectable products). Factors influencing use of the rectal route of administration are:
 - a. The ability to bypass first-pass metabolism. This depends on the part of the rectum absorbing the drug. The inferior and middle rectal veins drain the lower part of the rectum into the inferior vena cava and thus directly into the systemic circulation and bypass the liver.
 - b. Rectal dosage form – suppositories versus liquid
 - i. The rate and extent of absorption of certain drugs such as diazepam may be improved when solutions are used rather than suppositories.
 - ii. Suppositories as rectal dosage forms for drugs with a narrow therapeutic index may be impractical to use because of the need for individualized dosing on the basis of body weight in pediatric patients and the limited availability of different doses.
 - iii. Cutting of suppositories for drugs with a narrow therapeutic index may result in an unpredictable dose because uniform distribution of the drug throughout the suppository cannot be guaranteed.
 - iv. In the absence of a suitable rectal dosage form, oral liquids can be administered rectally if the oral or intravenous route is precluded. However, large-volume or high-osmotic concentrations of the oral liquid may cause premature evacuation of the bowel, resulting in erratic and incomplete delivery of the dose.
3. Intramuscular:
 - a. Factors that affect intramuscular absorption:
 - i. Intramuscular absorption varies in premature newborns because they have a smaller percentage of body weight as skeletal muscle and subcutaneous fat than older infants, children, and adults.
 - ii. The surface area over which the injected drug volume can be distributed. Reduced muscle mass may result in reduced intramuscular absorption because of decreased dispersion within the muscle mass. This may be significantly influenced by the type of intramuscular formulation (aqueous vs. nonaqueous), with nonaqueous formulations being slower to disperse.
 - iii. Blood flow to the injection site – Reduced muscle tone causing poor perfusion in premature neonates, full-term neonates, and infants will decrease absorption. Blood flow relative to the muscle mass is greater in young children than in adults, resulting in rapid absorption.
 - iv. Ease of penetration through the endothelial capillary walls
 - v. Muscle activity – Increased muscle activity will result in increased blood flow and may increase the surface area, thus increasing intramuscular absorption.
 - b. Intramuscular injections can be painful and should be used only when oral administration is not possible or intravenous access is unavailable (Table 3).

Table 3. Needle Length, Injection Site, and Volume for Intramuscular Injections in Children as Recommended by the Advisory Committee on Immunization Practices

Age	Injection Site	Needle Length	Maximum Injection Volume (mL)
0–28 days	Anterolateral thigh (vastus lateralis)	5/8 in. (16 mm)	0.5
Infants: 1–12 mo	Anterolateral thigh	1 in. (25 mm)	1
Toddlers, 1–2 yr	Anterolateral thigh (preferred)	1–1.25 in. (25–32 mm)	1–1.5
	Deltoid muscle of arm	5/8–1 in. (16–25 mm)	
Children, 3–10 yr	Deltoid muscle of arm (preferred)	5/8–1 in. (16–25 mm)	1.5–2
	Anterolateral thigh	1–1.25 in. (25–32 mm)	
Children, 11–18 yr	Deltoid muscle of arm (preferred)	5/8–1 in. (16–25 mm)	2.5–3
	Anterolateral thigh	1–1.25 in. (25–32 mm)	

4. Percutaneous absorption:

- a. Factors that increase percutaneous absorption:
 - i. Thinner and/or immature epidermis and stratum corneum, especially in premature neonates
 - ii. Increased skin hydration
 - iii. Body surface area (BSA) to weight ratio is higher in neonates, infants, and children than in adults – A greater amount of drug may be absorbed relative to their body weight.
 - iv. Damaged skin
- b. Toxic effects have been reported with topical agents such as EMLA (eutectic mixture of lidocaine and prilocaine) and hexachlorophene solution.

C. Distribution

1. Volume of distribution (Vd) represents the apparent volume into which the drug is distributed to provide the same concentration as is currently in blood plasma.
2. Factors determining the differences in drug distribution between neonates, infants, children, and adults are:
 - a. Proportion of body water
 - i. Total body water decreases from around 92% of body weight in a premature newborn to 75% in a full-term newborn to 60% (25% is extracellular water and 35% is intracellular) by 1 year of age.
 - ii. Total body water approaches adult values of 50%–60% (20% extracellular and 40% intracellular) by 12–13 years of age.
 - iii. As total body water decreases with age, the proportion of total body water as extracellular water also decreases (from around 60% in premature newborns to around 20% in adolescents).
 - iv. Proportion of total body water significantly affects the Vd of hydrophilic drugs.
 - v. Hydrophilic drugs such as aminoglycosides, β -lactam antibiotics, and digoxin distribute into the extracellular fluid and thus have a larger Vd relative to body weight (i.e., L/kg) in neonates than in older infants and children, requiring larger mg/kg doses to achieve the same serum concentrations.
 - vi. This principle should be applied cautiously in pediatric patients with obesity while calculating mg/kg doses because of the relatively lower percentage of extracellular water in obesity.
 - vii. In children with actual body weight (ABW) exceeding ideal body weight (IBW) by 125%, an adjusted body weight should be used to determine doses of drugs with a narrow therapeutic index such as aminoglycosides and digoxin. A commonly used formula for adjusted body weight assumes that 40% of the difference between the ABW and the IBW (adipose tissue) is indeed lean muscle mass.

$$\text{Adjusted body weight} = \text{IBW} + 0.4 (\text{ABW} - \text{IBW})$$

$$\text{IBW} = [(\text{height}^2) \times 1.65] \div 1000$$

where body weight is in kg and height is in cm (152.4 cm or less)

IBW for age younger than 18 years but height greater than 152.4 cm (60 inches or 5 feet):

$$\text{IBW (male over 5 feet)} = 39 + (2.27 \times \text{height inches over 5 feet})$$

$$\text{IBW (female over 5 feet)} = 42.2 + (2.27 \times \text{height inches over 5 feet})$$

For drugs such as aminoglycosides, serum concentrations should be measured with first doses, a Vd estimated, and the patient's dose individualized using these data despite not having reached steady state. This will avoid under- or overestimation of the dose and prevent therapeutic failure or toxicity, respectively.

- b. Total body fat
 - i. Total body fat increases from 12% to 16% of body weight at full-term to 20% to 25% at 1 year of age.
 - ii. A second period of increase occurs at 5–10 years of age, followed by a decrease in male adolescents at around age 17.
 - iii. At puberty, there is a rapid increase in the percentage of body fat in females, approaching twice the value of males.
 - iv. V_d relative to body weight for lipophilic drugs is larger in children and adults than in neonates and infants because of the higher percentage of body fat.
- c. Plasma proteins
 - i. Albumin, α_1 -acid glycoprotein, and lipoproteins are the important drug-binding proteins.
 - ii. Albumin makes up an average of 58% of all plasma proteins.
 - (a) Acidic and neutral drugs such as certain β -lactam antibiotics, warfarin, and phenytoin have great binding affinity for albumin.
 - (b) Basic compounds such as propranolol and alprenolol bind to α_1 -acid glycoprotein, lipoproteins, and β -globulins.
 - iii. Factors that affect binding of drugs to plasma proteins include:
 - (a) Total amount of proteins
 - (b) Number of binding sites
 - (c) Binding affinity
 - (d) Physiologic conditions (e.g., change in blood pH) or presence of endogenous compounds with higher protein-binding affinity (e.g., bilirubin, free fatty acids)
 - iv. These factors may increase the free, active fraction of highly protein-bound drugs, which can lead to enhanced effect or toxicity. For drugs such as phenytoin, which can be therapeutically monitored, dosing may be adjusted on the basis of free phenytoin concentrations.
 - v. Neonates have lower total plasma protein concentration and lower drug–protein-binding capacities, resulting in lower plasma protein binding of various drugs compared with the older population.
 - (a) The concentration, binding capacity and function of all proteins, including albumin and α_1 -acid glycoprotein approach adult values by 1 year of age and remain stable in healthy individuals 2–18 years of age.
 - (b) Neonates often have hyperbilirubinemia secondary to increased red cell destruction and decreased hepatic conjugation. The binding capacity of bilirubin to plasma albumin is decreased in this population. Drugs highly bound to the plasma proteins, such as the sulfonamides and ceftriaxone, may displace bilirubin from albumin-binding sites and contribute to kernicterus.

D. Metabolism

1. The liver is the primary organ involved in drug metabolism. However, certain enzymes used in drug metabolism by the liver are also secreted by the bacteria colonizing the intestinal flora and are thus partly responsible for drug metabolism. The liver's ability to metabolize drugs follows maturational development from a premature infant to an adult.
2. Drug metabolism is carried out by two different enzymatic reactions, phase I and phase II.
 - a. Phase I reaction:
 - i. Structurally alters the drug molecule by oxidative, reductive, or hydrolytic reactions by introducing or exposing a functional group and priming it for a phase II reaction.
 - ii. Oxidative enzymes include the CYP system, flavine-containing monooxygenases, monoamine oxidases, alcohol dehydrogenases, and aldehyde dehydrogenases.

- iii. Reductive enzymes include aldo-keto reductases and keto reductases. Data on the ontogeny of reductive enzymes in humans are limited.
 - iv. Hydrolytic enzymes include esterases, dehydropeptidases, and epoxide hydrolases.
 - v. Table 4 represents maturational differences in the development of these enzymes and their effects on drug metabolism.
- b. Phase II reaction:
- i. Primarily consists of enzymes responsible for conjugation of molecules formed from phase I reaction and converting them into a more water-soluble entity that can be easily excreted.
 - ii. These reactions and the enzymes involved consist of:
 - (a) Acetylation reaction by enzymes *N*-acetyltransferase (NAT) 1 and NAT2
 - (b) Methylation reaction by enzymes *N*-methyltransferase and thiol *S*-methyltransferase
 - (c) Glucuronidation reaction by enzyme isoforms uridine 5'-diphosphate glucuronosyltransferase (UGT) 1A1 (UGT1A1), UGT1A6, and UGT2B7
 - (d) Sulfation reaction by enzyme sulfotransferase
 - (e) Glutathione *S*-transferase

Table 4. Maturational Changes in Drug-Metabolizing Enzymes

Enzyme	Fetus	Neonate	Infant	Child	Adolescent	Applications in Patient Care
CYP1A2	Absent	Present	50% of adult values by 1 yr of age	Adult values at > 1 yr of age	Adult values	Decreased metabolism of theophylline and caffeine used in treatment of apnea. Metabolic clearance ~10 times lower than in adults
CYP2B6	Slightly higher than in adults	Increased, reaches adult values by 1 yr of age			Adult values	Nevirapine, a nonnucleoside reverse transcriptase inhibitor, has greater clearance in children than in adults Genetic polymorphism with significant clinical implications exists for this isozyme
CYP2C9	10% of adult values reached	30% of adult values reached	Reaches adult values by 1–6 mo of age	Higher than adult values (peak activity at 3–4 yr of age)	Decreases to adult values at puberty	Phenytoin weight-based dosing recommendations are highest between 6 mo and 3 yr of age and decreases to adult values by 10–16 yr of age Genetic polymorphism with significant clinical implications exists for this isozyme
CYP2C19	10% of adult values reached	30% of adult values reached	50%–70% of adult values reached by 6 mo of age	Higher than adult values (peak activity at 3–4 yr of age)	Decreases to adult values at puberty	Diazepam half-life increased in young infants (25–100 hr) compared with children (7–37 hr) and adults (20–50 hr). No effect on omeprazole Genetic polymorphism with significant clinical implications exists for this isozyme

Table 4. Maturational Changes in Drug-Metabolizing Enzymes (*continued*)

Enzyme	Fetus	Neonate	Infant	Child	Adolescent	Applications in Patient Care
CYP2D6	Minimal activity	30% of adult values reached	Adult values reached by 1 yr of age			Conversion of codeine to morphine is decreased in infants, resulting in lack of efficacy and poor pain control Genetic polymorphism with significant clinical implications exists for this isozyme
CYP3A4	Decreased	Decreased, 30%–40% of adult values	Adult values reached by 1 yr of age	Increased at 1–4 yr of age, then decreases to adult values	Adult values at puberty	Most abundant CYP enzyme in the human liver and intestine. Midazolam metabolism is reduced in premature infants but increases by 5-fold by 3 mo of age Activity altered by enzyme inducers and inhibitors
CYP3A5	Achieves activity similar to neonatal period by third trimester	Activity maturation independent of age				Overlaps with CYP3A4 in metabolizing drugs Has larger interindividual variability because of genetic polymorphism (e.g., tacrolimus, vincristine)
CYP3A7	Highest activity among CYP3A enzymes	Decreased	Minimal			Primary CYP3A isoform at birth but decreases after first month of life with concurrent increase in CYP3A4 activity called “developmental switch.” Fenoldopam and famciclovir were found to be CYP3A7 substrates in vitro
ADH1A1	Present	Increases with age; activity is ~60% higher than in adults				Of the ADHs, ADH1A is involved in drug metabolism – Changes an active cyclophosphamide metabolite to inactive. Adults have decreased ADH1A activity compared with children early in childhood
ALDH1A1	Unknown	3 times lower than in adults				Of the ALDHs, ALDH1A1 is involved in drug metabolism – Converts cyclophosphamide metabolite to inactive metabolites, increasing the risk of cyclophosphamide-induced hepatotoxicity in the younger population
CES1	Lowest activity	10 times higher activity than in the prenatal stage	Rate of increase in enzyme activity slows down; still almost twice the neonatal stage increasing until 18 yr of age			CES1 is required to convert oseltamivir to its active carboxylate metabolite. However, oseltamivir dosing is also influenced by renal clearance of the carboxylate (higher clearance in children 1–12 yr of age)

Table 4. Maturational Changes in Drug-Metabolizing Enzymes (*continued*)

Enzyme	Fetus	Neonate	Infant	Child	Adolescent	Applications in Patient Care
CES2	Lowest activity	Increase in activity follows increase in age. Adult values are ~50 times higher than in the prenatal stage				CES2 is also present outside the liver in the duodenum and the jejunum and shows similar increase in activity with age. CES2 is required to convert irinotecan, a topoisomerase II inhibitor antineoplastic agent used in treating pediatric solid tumors, to its active metabolite SN-38
UGT	10%–20% of adult activity	Decreased	25% adult activity reached by 3 mo of age	Adult value reached by 6 mo to 3 yr of age	Adult values	Metabolism of acetaminophen by glucuronidation increases with age. The younger the age, acetaminophen is predominantly excreted as a sulfate conjugate by sulfotransferases. The ratio of glucuronide conjugate to sulfate increases from 0.34 in a newborn to 0.8 in a child 3–10 years of age, from 1.61 in adolescence to 1.8–2.3 in adults
Sulfo-transferases	Present	Decreased	Increased for certain substrates	Increased for certain substrates	Activity 3 times lower than during childhood for certain substrates	See above example of acetaminophen
TPMT	30% of the adult value	Characterization of maturational changes in TPMT is confounded by effect of sex and genetic polymorphism				Mercaptopurine is metabolized by TPMT Genetic polymorphism with significant clinical implications exists for this enzyme

ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase; TPMT = thiopurine S-methyltransferase; UGT = uridine 5'-diphosphate glucuronosyltransferase.

E. Elimination

- Chemicals and drugs are primarily excreted by the kidneys in the urine. In addition, these may be excreted by bile into the feces.
- Other routes of elimination include sweat, saliva, tears, and milk. Gaseous molecules undergo pulmonary excretion by breath.
 - Urinary excretion occurs as glomerular filtration (GF), tubular secretion, and tubular reabsorption.
 - Nephrogenesis occurs until 36 weeks' GA, with significant glomerular development occurring at 34–36 weeks' GA.
 - Renal tubules do not mature anatomically or functionally at the same rate as the glomeruli, and maturation is significantly delayed, even in full-term neonates.
 - Renal blood and plasma flow increases with age as cardiac output increases and peripheral vascular resistance decreases. At birth, it is low at 12 mL/minute, increasing to 140 mL/minute by 1 year of age.

- e. Drug excretion by GF:
- Elimination of drugs through GF is a passive process influenced by GFR and binding of the drug to plasma proteins.
 - GFR increases with increasing renal blood flow. A preterm newborn (29–34 weeks' GA) has an approximate GFR of 15 mL/minute/1.73 m² at 7 days postnatal age (PNA). In a full-term newborn (38–42 weeks' GA), it approximates 40 mL/minute/1.73 m² at 7 days PNA, increasing to adult values of 100 mL/minute/1.73 m² by 3 months of age. It may exceed adult values thereafter.
 - Drug excretion increases with increasing GFR but is decreased for drugs that are extensively protein bound.
 - Renally eliminated drugs need dose adjustments as the GFR decreases. GFR can be assessed using different methods.
 - Methods of estimating GFR
 - GFR can be estimated using the inulin clearance method or the renal clearance of a radio-pharmaceutical technetium-99m diethylenetriaminepentaacetic acid (Tc-99m DTPA). Both inulin and Tc-99m DTPA are excreted entirely by GF and are considered the “gold standard” in estimating GFR. However, they are labor-intensive, time-consuming, and expensive and expose the patient to a radioactive molecule.
 - GFR can be estimated by calculating CrCl because SCr is excreted primarily by GF. CrCl can be determined by a 24-hour urine collection and measuring SCr.
$$\text{CrCl (mL/min/1.73 m}^2\text{)} = (\text{Cr}_u \times V \times 1.73) / (\text{SCr} \times T \times A)$$
where Cr_u = urine Cr concentration (mg/dL), V = total urine volume collected during sampling period (mL), SCr = serum creatinine (mg/dL), T = duration of sampling period (min) (24 hr = 1440 min), and A = body surface area (m²).
 - Using SCr and a mathematical formula such as the bedside Schwartz equation is the least invasive, least expensive, and most expedient way to determine GFR.
$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 0.413 \times (L / \text{SCr})$$
where L = height or length (cm) and SCr = serum creatinine (mg/dL).
 - The original Schwartz equation used an empiric constant that varied by patient age and sex. With the change in SCr assay method to isotope dilution mass spectrometry, the bedside Schwartz equation was validated and is used clinically to determine eGFR in individuals 1–18 years of age.
 - The bedside Schwartz equation has not been validated in infants younger than 1 year. Change in SCr values over time and urine output must be used to determine renal function in this population. Urine output less than 0.5 mL/kg/hour for 6–12 hours is considered stage 1 acute kidney injury. In a newborn, SCr values may reflect maternal values for at least a week after birth.
 - Limitations of using SCr and therefore CrCl as a measure of GFR include changes in SCr values on the basis of age, sex, and muscle mass. It also depends on nutritional status and physical activity. In chronic renal failure, clearance of plasma creatinine by tubular secretion increases as GFR decreases; therefore, SCr values may be in the normal range despite decreased GFR.
 - Most pediatric drug dosing references provide recommendations for altered renal function using eGFR values in mL/minute/1.73 m². However, some drugs may require calculation of a nonnormalized (raw) eGFR to assist in renal dosing. For example, fos-carnet renal dose adjustment is made using CrCl values in mL/minute/kg. Multiplying the mL/minute/1.73 m² value with the patient's BSA and dividing it by 1.73 would convert the normalized eGFR into nonnormalized (mL/minute). The mL/minute/kg value is obtained by dividing mL/minute with the patient's body weight.

- (d) Other low molecular proteins such as cystatin C have been used to determine GFR. Plasma cystatin C values are independent of age, sex, height, weight, and muscle mass.

Cystatin C–based equation

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 70.69 \times (\text{cystatin C})^{0.913}$$

where cystatin C is in mg/dL.

Creatinine-cystatin C–based chronic kidney disease equation

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 39.8 \times [\text{ht/SCr}]^{0.456} \times [1.8/\text{cystatin C}]^{0.418} \times [30/\text{BUN}]^{0.079} \times [1.076^{\text{male}}] [1.00^{\text{female}}] \times [\text{ht}/1.4]^{0.179}$$

where ht = height in cm, SCr = serum creatinine in mg/dL, and BUN = blood urea nitrogen in mg/dL.

- f. Drug excretion by tubular secretion: This occurs through the proximal convoluted tubules and is an active or energy-dependent process.
- The proximal tubules are smaller than the glomeruli in a newborn. Development of the renal tubular function lags behind GFR.
 - Renal tubular function may approach adult values by 7–12 months of age. It can subsequently exceed adult capacity at 3–12 years of age. For example, the renal clearance of imipenem/cilastatin is almost twice the CrCl compared with the adult population, indicating significant tubular secretion in this population.
- g. Drug excretion and renal tubular reabsorption:
- Renal tubular reabsorption achieves adult values by 2 years of age and is last in maturation of renal function. It occurs by passive diffusion.
 - Drugs with significant renal tubular reabsorption may have delayed clearance and increased serum concentrations.
- h. Drug excretion by renal transporters: These include P-gp, organic anion transporters (OATs), and organic cation transporters.
- Renal P-gp transporters are present during early fetal life (11–14 weeks' GA) and reach adult values by birth. P-gp interacts with hydrophobic compounds and transports it using ATP and intrinsic ATPase energy.
 - The OAT family removes anionic molecules such as nonsteroidal anti-inflammatory and antibiotics by transport mechanisms present in the basolateral membrane of the renal epithelial cells. Their maturity is low at birth, increases over the first few weeks of life, and then decreases to adult values.

Patient Cases

1. As a pediatric pharmacy expert, you are consulting with a pharmaceutical company wanting to develop a new drug with a pediatric indication and a narrow therapeutic index as a rectal dosage form. Which concept regarding rectal drug absorption would be most relevant in developing this dosage form?
 - A. Using a rectal dosage form would offer higher bioavailability irrespective of the part of the rectum absorbing the drug because it significantly avoids first-pass metabolism.
 - B. Because the drug has a narrow therapeutic index, individualized dosing will be necessary, and developing a suppository as a rectal dosage form might be impractical.
 - C. With a narrow therapeutic index, individualized dosing can still be provided by cutting suppositories into appropriate sizes according to the dose required.
 - D. Designing an oral liquid formulation would be more appropriate because it can also be administered rectally when needed.

Questions 2 and 3 pertain to the following case.

You are training a new hire who has extensive inpatient pharmacy experience in an adult hospital. You are training the new hire to verify ampicillin and gentamicin orders for B.C., a 30-week GA newborn.

2. Which difference between premature neonates and adults when determining the correct gentamicin dose would you most expect the trainee to know?
 - A. The changes in V_d and clearance have equal opposite effects on half-life, resulting in similar half-lives in neonates and adults.
 - B. V_d 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.
3. Your trainee is trying to calculate B.C.'s eGFR. Which would be best to include in educating the trainee about calculating the eGFR in B.C.?
 - A. The bedside Schwartz equation is usually used to calculate an eGFR according to the patient's height and SCr value.
 - B. The original Schwartz equation can be used because it was validated for populations younger than 1 year.
 - C. 24-hour urine collection and SCr can be used.
 - D. Serial changes in SCr over time and urine output can be used.
4. P.D. is a 10-day-old term infant in the neonatal ICU being treated for seizures. P.D. continues to have seizures despite phenobarbital therapy with a therapeutic phenobarbital concentration of 28 mcg/mL. The medical intern wants to prescribe a loading dose and then begin a maintenance dose of phenytoin. Which is most appropriate 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 have phenytoin-induced liver toxicity.

Patient Cases (*continued*)

5. B.G. is a 2-year-old (weight 12 kg) with a methicillin-resistant *Staphylococcus aureus* 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. The high renal clearance and short half-life of vancomycin in children would 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 initiated on the adult equivalent dose of 15 mg/kg every 12 hours.

III. PHARMACODYNAMICS

- A. Definition: Pharmacodynamics represents what a drug does to an individual or a body function. Individual drug effects vary, but pediatric compared with adult pharmacodynamics are characterized by differences in receptors, disease etiology, paradoxical effects of drugs, altered toxicity, and direct drug effects on growth and development (Table 5).
- B. Altered drug responses may be caused by the following drug receptor differences.
 - 1. 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.
 - 2. Affinity – Pediatric patients' receptors may have a greater affinity for drugs.
 - 3. Numbers – Pediatric patients may have fewer receptors.
 - 4. Paradoxical drug effects may occur in children. An example of a commonly described effect in some children are the excitatory consequences associated with antihistamines, rather than the more typical sedation.
 - 5. Drugs may affect growth and development.
 - a. Corticosteroids
 - b. Topiramate
 - c. Tetracycline
 - d. Growth hormone
 - e. Drugs that affect appetite
- C. Assessment of Pharmacodynamics and Disease Dynamics in Pediatric Patients
 - 1. 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).
 - 2. Normal ranges and therapeutic goals may be different (e.g., blood pressure, heart rate, CD4⁺ cells).
 - 3. Etiology and pathophysiology of diseases (e.g., hypertension – usually secondary, febrile seizures, neonatal apnea/bradycardia, CNS bleeds)

4. Diseases and toxicities exclusive to pediatric patients (e.g., Kawasaki disease, Reye syndrome, patent ductus arteriosus [PDA], absence epilepsy, many childhood cancers)
5. Altered disease dynamics (hypoxemia-induced neonatal seizures and PDA often have rapid healing, whereas untreated HIV infection has very rapid progression)

Table 5. Selected Known Pediatric-Specific Adverse Drug Reactions and Recommendations

Drug	Reaction	Recommendations
Antidepressants	An increased risk of suicide among adolescents has been reported Sudden cardiac death (tricyclic)	Antidepressants should be used with caution in children and adolescents Avoid in children (desipramine) Use with caution (imipramine)
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
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
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
Fluoroquinolones (FQs) drug class	Development of permanent lesions of the cartilage of weight-bearing joints and other signs of arthropathy in immature animals have 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 limited tissue perfusion with other antibiotics
Glucocorticoid steroids Topical corticosteroids (medium, high, and very high potency)	Contribute to slow growth in children. Systemic dexamethasone use in infants is associated with reduced head circumference and increased cerebral palsy Absorption of topical steroids – children > adults; can cause adrenal suppression	Limit systemic steroid use to the lowest dose and duration, if possible Use topical steroids with caution when treating diaper dermatitis in infants < 1 yr of age

Table 5. Selected Known Pediatric-Specific Adverse Drug Reactions and Recommendations (*continued*)

Drug	Reaction	Recommendations
Macrolide antibiotics (azithromycin, erythromycin)	Hypertrophic pyloric stenosis	Avoid in neonates Use in treating <i>Bordetella pertussis</i> with azithromycin and <i>Chlamydia trachomatis</i> with either of the macrolides permitted Risk-benefit consideration in treating ureaplasma (azithromycin)
Nitrofurantoin	Hemolytic anemia	Avoid in neonates
Olanzapine	Weight gain, hyperglycemia, hyperlipidemia (metabolic syndrome)	Long-term use (> 24 wk) in children should be avoided
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 (e.g., IV lorazepam). Avoid doses > 3 g/day in neonates. Use doses > 34 mg/kg/day with caution in neonates
Phenothiazine drug class (e.g., promethazine)	A risk of severe respiratory depression has been reported in this class of drugs	Use in children < 2 yr of age is contraindicated
Sodium phosphate solution (rectal) (enema)	Electrolyte abnormalities, arrhythmias, death	Avoid in infants
Sulfonamide drug class, dicloxacillin, cefoperazone, and ceftriaxone	Kernicterus was reported in neonates with hyperbilirubinemia receiving drugs that displace bilirubin from protein-binding sites in the blood, 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 infants with jaundice. Sulfonamides should be avoided in neonates and infants. Oral doses of sulfamethoxazole and trimethoprim are unlikely to cause kernicterus
Tetracycline drug class (demeclocycline, tetracycline)	Dental staining and darkening of permanent teeth has been reported in patients receiving tetracyclines during the time of tooth crown formation. Premature neonates may have retardation of skeletal and bone growth (tetracycline)	Tetracycline drugs are contraindicated in pregnant women, nursing mothers, and children < 8 yr Doxycycline is not associated with these adverse effects
Valproic acid	Valproic acid–associated hepatotoxicity has its highest risk in children < 2 yr. It is caused by several pharmacokinetic 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 of age receiving valproic acid
Lopinavir/ritonavir	Serious cardiovascular events (bradycardia, heart block, heart failure) and renal failure 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
Verapamil	Asystole	Avoid in < 1 yr of age
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

IV = intravenous(ly); PMA = postmenstrual age; UGT = uridine 5'-diphosphate glucuronosyltransferase.

IV. PHARMACOGENOMICS

A. Definitions:

1. Pharmacogenomics: Field of genetics that characterizes the way in which a person's genetic profile can influence the way he or she responds to drug therapy
2. Genes: Specific sequence of nucleotides (adenine, cytosine, guanine, and thymine) that carries the code for specific proteins or segments of protein that have different functions in the body
3. Genotype: A particular version of the DNA sequence (gene) an individual has at a locus
4. Phenotype: An observable trait such as eye or hair color because of the individual's specific genomic makeup or genotype
5. Allele: Consists of single base pair or a segment of base pairs at a specific genomic location on the chromosome. If the base pairs or the sequence is identical on both chromosomes, the individual is homozygous for that allele and heterozygous if they are different. Each person inherits one allele from each parent.
6. Mutation: A change in the DNA sequence that may alter the gene function. It can occur because of errors in DNA replication during cell division or exposure to mutagens or viral infections. It can arise in the ovum or the sperm (germline mutation) and be passed on to the offspring or in body cells (somatic) that are not passed on to the offspring.
7. Genomic variation (variants): Differences in specific DNA sequence among individuals or populations
8. Polymorphism: Two or more variant forms of a specific DNA sequence that can occur among different individuals or populations. Variation at a single nucleotide (single nucleotide polymorphism) is the most common type of polymorphism. Others may involve more than a single nucleotide – large sequences of DNA.

B. Pharmacogenomics can be used in optimizing efficacy (identifying responders and nonresponders) and safety (avoiding adverse effects) of drug therapies on the basis of the patient's genotype (Table 6).

1. This information is included in individual drug labeling as approved by the FDA. Guidance on changes in drug dosing or monitoring for toxicity is provided, when available, according to the patient's pharmacogenomic biomarkers.
2. The Table of Pharmacogenomic Biomarkers in Drug Labeling available at the FDA website currently lists over 400 drugs with a link to labeling texts. Much of this information has been derived from adult studies.
3. These biomarkers consist of germline or somatic gene variants (polymorphism, mutations), genomic variation causing functional deficiencies, differences in gene expression, and chromosomal abnormalities. These are in humans only.

Table 6. Pharmacogenomic Biomarkers Influencing Efficacy and Safety of Drug Therapies

Drug	Biomarker	Labeling Recommendation
Abacavir	HLA-B	• Risk of multiorgan failure and anaphylaxis because of abacavir in patients carrying the <i>HLA-B*5701</i> allele to abacavir • Patients should be screened for the <i>HLA-B*5701</i> allele • Abacavir is contraindicated in <i>HLA-B*5701</i>-positive patients
Allopurinol	HLA-B	• Patients carrying the <i>HLA-B*5801</i> allele are at a higher risk of allopurinol hypersensitivity syndrome • Testing for this allele should be considered in genetically at-risk populations (African, Asian)
Aripiprazole	CYP2D6	• CYP2D6 poor metabolizers have high aripiprazole concentrations • Dose adjustments recommended

Table 6. Pharmacogenomic Biomarkers Influencing Efficacy and Safety of Drug Therapies (*continued*)

Drug	Biomarker	Labeling Recommendation
Azathioprine	TPMT, NUDT15	- TPMT and/or NUDT15 deficiency may cause severe, life-threatening myelotoxicity - Testing for these deficiencies recommended - Homozygous for either deficiency – Consider alternative therapy - Heterozygous for either deficiency – Consider dose reduction - Heterozygous for both deficiencies – Substantial dose reduction may be necessary
CBZ	HLA-B	- Strong association between the risk of developing SJS/TEN from CBZ and the presence of the <i>HLA-B*1502</i> allele - At-risk populations (ancestry across broad areas of Asia) should be screened before initiating CBZ - Initiate CBZ only if the benefits outweigh the risks
CBZ	HLA-A	- Hypersensitivity reactions (SJS/TEN, maculopapular eruptions, and DRESS) reported in patients with the <i>HLA-A*3101</i> allele - Initiate CBZ only if the benefits outweigh the risks
Carvedilol	CYP2D6	CYP2D6 poor metabolizers have a higher rate of dizziness as the dose is titrated, presumably from the vasodilating effects of the higher concentrations of the α-blocking R (+) enantiomer
Celecoxib	CYP2C9	- Adult poor metabolizers – Initiate with one-half the lowest recommended dose - Pediatric juvenile rheumatoid arthritis poor metabolizers – Alternative treatment recommended
Citalopram	CYP2C19	- Poor metabolizers – Steady-state C_{max} and AUC increased by 68% and 107%, respectively - Daily doses cannot exceed 20 mg in order to prevent QTc prolongation
Clonazepam	CYP2C19	Poor metabolizers – Concentrations of active metabolite, <i>N</i>-desmethyloclobazam higher, dose modification recommended
Clopidogrel	CYP2C19	- Clopidogrel converted to an active metabolite by CYP2C19 enzyme that inhibits platelet aggregation - Poor metabolizers form less of the active metabolite and have reduced effect on platelet activity at recommended doses - Alternatives should be considered
Codeine	CYP2D6	Ultra-rapid metabolizers of CYP2D6 - Rapidly and completely convert codeine to active metabolite, morphine - Higher-than-expected serum morphine concentrations - Life-threatening and fatal respiratory depression or signs of overdose possible at recommended doses - Codeine not recommended in these patients Poor metabolizers may not have adequate pain control
Dolutegravir	UGT1A1	<i>UGT1A1</i> polymorphism – Poor dolutegravir metabolism decreased clearance, increased AUC
Efavirenz	CYP2B6	<i>CYP2B6*6/*6</i> genotype – A 2-fold increase in C_{max} resulting in QTc prolongation
Elexacaftor, ivacaftor, and tezacaftor	CFTR	- Combination used only in patients with cystic fibrosis $\geq$ 12 yr who have at least one F508del mutation in the <i>CFTR</i> gene - Presence of at least one F508del mutation should be confirmed before initiating this
Proton pump inhibitors	CYP2C19	- Poor metabolizers of CYP2C19 – Steady-state AUC twice the AUC achieved in extensive metabolizers. Standard dosing for acute use; dose reduction recommended for chronic use of proton pump inhibitors - Ultra-rapid metabolizers: Consider using at 100%–300% of starting dose

Table 6. Pharmacogenomic Biomarkers Influencing Efficacy and Safety of Drug Therapies (*continued*)

Drug	Biomarker	Labeling Recommendation
Fluorouracil	DPYD	- Fluorouracil is catabolized by the enzyme DPD - Decreased DPD activity can result in shunting fluorouracil to the anabolic pathway, leading to mucositis, diarrhea, neutropenia, and neurotoxicity - No dose of fluorouracil has been found safe in those with complete DPD deficiency - Fluorouracil should be held or permanently discontinued depending on onset, duration, and severity of the symptoms
Fosphenytoin Phenytoin	CYP2C9	- Intermediate or poor CYP2C9 metabolizers (e.g., $*1/*3$, $*2/*2$, $*3/*3$) – Increased phenytoin serum concentrations requiring lower doses - Known carriers of the decreased-function $CYP2C9*2$ or $*3$ alleles – Consider starting at the low end of the dose range; monitor serum concentrations to maintain total phenytoin concentrations of 10–20 mcg/mL
Fosphenytoin Phenytoin	HLA-B	<i>HLA-B*1502</i> is a genetic marker for increased risk of developing SJS/TEN in patients of Asian ancestry taking antiepileptic drugs associated with SJS/TEN, including phenytoin
Irinotecan	UGT1A1	- Increased risk of neutropenia in patients who are homozygous for the $UGT1A1*28$ allele ($UGT1A1$ 7/7 genotype) - Dose reduction should be considered, but the amount of reduction is not known - UGT1A1 also mediates glucuronidation of SN-38 to inactive glucuronide metabolite SN-38G - In vitro, SN-38 has 50–100 times more cytotoxicity than SN-38G
Mercaptopurine	TPMT, NUDT15	- TPMT and/or NUDT15 deficiency may cause severe, life-threatening myelotoxicity - Testing for these deficiencies recommended - Homozygous for either deficiency – Consider alternative therapy - Heterozygous for either deficiency – Consider dose reduction - Heterozygous for both deficiencies – Substantial dose reduction may be necessary
Oxcarbazepine	HLA-B	- Strong association between the risk of developing SJS/TEN from oxcarbazepine and the presence of the <i>HLA-B*1502</i> allele (Asian ancestry) - Screen at-risk populations for this allele before initiating oxcarbazepine - Initiate only if the benefits outweigh the risks
Tacrolimus	CY3A5	- Poor metabolizers (nonexpressers): Use standard dose followed by TDM - Normal, intermediate, and extensive metabolizers (expressers) need ~1.5–2.5 times the standard dose with TDM - These recommendations are not included in the product labeling
Thioguanine	TPMT, NUDT15	- Deficiency of TPMT and/or NUDT15 may cause severe, life-threatening myelotoxicity; testing recommended - Homozygous for either deficiency: Consider dose reduction to 10% or less of the standard dose - Heterozygous for either enzyme: Consider dose reduction depending on tolerability - Heterozygous for both deficiencies: Substantial dose reduction may be necessary
Tramadol	CYP2D6	Ultra-rapid metabolizers of CYP2D6 - Tramadol converted to high, potentially life-threatening active metabolite, <i>O</i>-desmethyltramadol, which can cause fatal respiratory depression or overdose (extreme sleepiness, confusion, or shallow breathing) - These patients should not receive tramadol

Table 6. Pharmacogenomic Biomarkers Influencing Efficacy and Safety of Drug Therapies (*continued*)

Drug	Biomarker	Labeling Recommendation
Voriconazole	CYP2C19	Heterozygous poor metabolizers • Voriconazole exposure ~4-fold higher than their homozygous extensive metabolizer counterparts • Choose alternative antifungal • If voriconazole indicated, initiate at 50% of standard dose and TDM necessary Heterozygous rapid metabolizers • > 18 yr of age: Choose alternative antifungal • < 18 yr of age: Standard dosing with TDM
Warfarin	CYP2C9, VKORC1	• Variant alleles, <i>CYP2C9</i>*2 and <i>CYP2C9</i>*3, result in decreased in vitro CYP2C9 enzymatic 7-hydroxylation of <i>S</i>-warfarin • Warfarin reduces the regeneration of vitamin K through inhibition of VKOR, a multiprotein enzyme complex • Certain single nucleotide polymorphisms in the <i>VKORC1</i> gene (e.g., -1639G>A) have been associated with variable warfarin dose requirements. See specific dosing recommendations in those who have these variant alleles

CBZ = carbamazepine; CFTR = cystic fibrosis transmembrane conductance regulator; DPD = dihydropyrimidine dehydrogenase enzyme; DRESS = drug reaction with eosinophilia and systemic symptoms; NUDT15 = nucleotide diphosphatase enzyme; SJS = Stevens-Johnson syndrome; TDM = therapeutic drug monitoring; TEN = toxic epidermal necrolysis; TPMT = thiopurine S-methyltransferase; UGT1A1 = uridine 5'-diphosphate glucuronosyltransferase 1A1; VKORC = vitamin K epoxide reductase complex.

V. COMPOUNDED DRUG FORMULATIONS FOR THE PEDIATRIC POPULATION

A. Scope of Need:

1. According to a National Health and Nutrition Examination Survey conducted by the National Center for Health Statistics, 19.8% of children (786 of 4404) younger than 19 years were taking at least one prescription medication during 2013–2014. Of these, 13.9% (586 of 4404) used medications for chronic health conditions and 7.1% for an acute health condition (used less than 30 days). The 13- to 19-year-old age group had the highest total number of medications (22.8%) and chronic medications (17.6%). The number of medications for acute health conditions was highest in the 0- to 5-year-old group at 9.1%. The 0- to 5-year-old group would most likely need an extemporaneously compounded formulation.

B. Reasons for Use of Compounded Drug Formulations in Children:

1. Pediatric drug doses are calculated using body weight (mg/kg) or BSA (mg/m²); therefore, doses are highly individualized, with no commercially available dosage form providing that dose.
2. A liquid dosage form is needed in those unable to swallow solid dosage forms or those who use a nasogastric or gastrostomy tube for medication administration, which is unavailable commercially.
3. For drugs requiring monitoring of serum concentrations, dose adjustments may result in doses commercially unavailable, necessitating compounding of the liquid dosage form.
4. A liquid dosage form may need to be compounded despite being commercially available as a liquid if the type or concentration of the inactive ingredient(s) could cause an adverse event, especially in premature or term neonates (e.g., dexamethasone intensol, which has 30% alcohol).
5. The above needs are met by extemporaneously compounding a liquid formulation of a suitable concentration using a commercially available solid dosage form. This is nonsterile compounding.

6. Individualized intravenous doses may need to be compounded extemporaneously for drugs commercially available at high concentrations that prevent the accurate measurement of small doses required in neonates and infants. This compounding must be done under sterile conditions. These doses may require further dilution. For example, furosemide injection is commercially available in a 10-mg/mL concentration. A 1-mg/kg dose of furosemide for a child weighing 750 g would be 0.75 mg or 0.075 mL of the undiluted medication, which would be impossible to prepare accurately without further dilution.
7. The most common extemporaneous formulation compounded for children would be a liquid solution or suspension for oral or enteral administration.

C. Compounding Oral Extemporaneous Formulations:

1. Informational resources needed:
 - a. United States Pharmacopeia (USP) contains official monographs of formulations complete with the list of ingredients needed to compound, stepwise method of compounding, storage conditions, and beyond-use date.
 - b. Prescribing information or package inserts of the brand name solid dosage forms of drugs with pediatric labeling may also provide this information.
 - c. Investigators' brochures or reports for marketed drugs may provide a recipe and beyond-use date. However, availability may be limited because of their proprietary and confidential nature. The formulation should not be used for routine patient care if stability, bioavailability, or bioequivalence trials are ongoing.
 - d. Primary peer-reviewed publications can be a source stability data. These publications can be obtained in PubMed using search terms *extemporaneous* or *compounding* or combining one or both of these terms with the drug name.
 - e. Tertiary references such as the *Pediatric and Neonatal Dosage Handbook*, *Pediatric Drug Formulations*, and *Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients* compile and publish information needed to extemporaneously compound a drug formulation.
2. Preparation of extemporaneous formulations:
 - a. A comprehensive review of preparing safe and effective extemporaneous formulations is found in the most current USP or by technical bulletins published by the American Society of Health-System Pharmacists.
 - b. Suspension is the most common extemporaneous formulation compounded because most drugs (active ingredients) and/or the inactive ingredients present in the solid dosage form used to compound from are water insoluble.
 - c. The vehicle used usually consists of a combination of a suspending agent and a sweetening agent in a 1:1 proportion.
 - d. Ora-Plus (Paddock Laboratories) is a commercially available ready-to-use carboxymethylcellulose-containing suspending agent, and Ora-Sweet (Paddock Laboratories) is a sweetening agent. They are usually mixed in a 1:1 proportion to prepare the vehicle. Ora-Sweet SF (Paddock Laboratories), a sugar-free syrup vehicle, can be used instead of Ora-Sweet. All three have an acidic pH, which should be considered in compounding suspensions when drug stability data are unavailable for the preparation.
 - e. Ora-Blend and Ora-Blend SF, marketed by the same manufacturer, are sweetened (with sugar or sugar free) suspending agents, eliminating the need to prepare a 1:1 mixture of Ora-Plus with Ora-Sweet or Ora-Plus with Ora-Sweet SF. Other available vehicles include SyrSpend SF (Fagron, Global), SyrSpend SF Alka, SyrSpend SF pH4, SyrSpend SF Cherry, SyrSpend SF Alka Cherry, SyrSpend SF Grape, and SyrSpend SF Alka Grape.

- f. If a ready-to-use suspending vehicle is unavailable, a vehicle consisting of a combination of methylcellulose 1% suspension with Simple Syrup USP in a 1:1 proportion can be prepared extemporaneously. This vehicle is inert and nonreactive and has a neutral pH of 6–8. However, the process of making methylcellulose 1% suspension is time-consuming and tedious.
 - g. Characteristics such as taste, odor, palatability, texture, color, and sweetness greatly influence a patient's acceptance of the preparation. Flavoring agents may be added to strategically mask the taste of the active ingredient. A variety of flavoring agents and information on how to mask a particular taste are commercially available (e.g., YummyMeds, FlavorRx). Coloring agents can also be added to improve the formulation's aesthetic appearance.
 - h. Caution should be used when adding a flavoring or coloring agent if it was not included in the original formulation with stability data. Coloring agents are sensitive to the formulation pH, presence of oxidizing or reducing substances, or exposure to light and are infrequently used. In the absence of stability data and the need to add a flavoring or coloring agent, it can be added to the dose right before administering it.
 - i. Other agents may be added to the formulation such as a solubilizing agent, an acid, or a base to adjust the pH of the formulation to enhance the stability.
 - j. Rarely, powder papers are compounded using dosage forms intended for adults with or without alterations. This is time-consuming and labor-intensive. In addition, the contents of the powder paper may still have to be reconstituted into a liquid or mixed with food such as applesauce before administration.
 - k. Solid dosage forms without an extemporaneous formulation can also be administered by splitting or crushing a tablet or opening a capsule and administering the content mixed with food. These methods can compromise the physicochemical stability of the drug, resulting in an altered rate of drug absorption or improper dosing secondary to inaccurate splitting of tablets or spillage during reconstitution. Mixing with a large amount of food is avoided because the patient may be unable to ingest the entire portion, which may result in inadequate dosing. If the dosage form contains a water-soluble active ingredient, the crushed tablet or the contents of the capsule can be mixed with a fixed amount of water. Knowing the milligrams per milliliter, an exact amount of dose can be obtained. However, this process has the potential for calculation errors.
3. Factors affecting clinical use of extemporaneous formulations: Stability and sterility
- a. The stability of an extemporaneous formulation is its ability to retain the characteristics and properties it had at the time of preparation throughout its storage and use (i.e., shelf life).
 - b. This consists of physical, chemical, microbiological, therapeutic, and toxicological stability during its shelf life.
 - c. These characteristics are affected by temperature, radiation, light, humidity, particle size, pH, water and other solvents, container properties, and other chemicals that may be present in the formulation.
 - d. All compounded preparations require a beyond-use date labeling (i.e., the date beyond which a compounded preparation is not to be used, which is determined from the date of preparation). The characteristics listed earlier determine this beyond-use date.
 - e. The beyond-use date of the extemporaneous formulation cannot be directly extrapolated from the expiration date of the commercially manufactured dosage form used to compound.
 - f. Physical stability is tested by storing the compounded formulation at various commonly used storage conditions (temperatures and containers). Common storage temperatures include room temperature (20°C–25°C), refrigerated temperature (2°C–8°C), and freezer temperature (-25°C to -20°C). Amber plastic prescription bottles are commonly used to store the formulation unless a different storage container is specified in the stability studies. Periodically (e.g., at weeks 0, 1, 2, 4, 8, and 12), the formulations are examined for physical stability, which includes lack of change in color, odor, taste, texture, and consistency of the preparation.

- g. The chemical stability of extemporaneous formulations is documented by measuring the concentration of the active ingredient(s) to ensure its potency during storage and use at simulated storage conditions. No more than a 10% change in the active ingredient concentration from the baseline (original) concentration should occur. In general, formulations with storage conditions and beyond-use dates, which preserve the potency of the active ingredient(s) within 90%–110% of the initial concentration, should be used; however, the USP monograph for the specific drug should be consulted for acceptable variance for each active ingredient being evaluated. When published stability studies for a drug provide several beyond-use dates, a recipe with the longest beyond-use date, ingredients, and storage conditions easily duplicated at the pharmacist's institution is chosen. However, a formulation reporting greater than 110% of the original concentration of active ingredient should not be chosen, even if it has the longest beyond-use date. The higher-than-original concentration in the formulation is most likely a result of physical instability (clumping or inadequate suspension) of the active ingredient in the formulation.
- h. When stability information is unavailable, USP-recommended beyond-use dates for general non-sterile compounded products should be used. For water-containing formulations prepared from solid ingredients, the USP-recommended beyond-use date is no later than 14 days when stored at cold temperatures of 2°C–8°C. This recommendation does not guarantee that the active ingredient will undergo no more than a 10% change in its concentration. For example, captopril (0.75 mg/mL) in cherry syrup is only stable for 2 days at room temperature or when refrigerated, and it is stable for 10 days or less in a 1:1 mixture of Ora-Sweet and Ora-Plus or Ora-Sweet SF and Ora-Plus, depending on the storage temperature. Thus, without the stability data, labeling these captopril formulations with a beyond-use date of 14 days according to the USP would be inappropriate.
- i. Updates to the USP general chapters on compounding nonsterile and sterile preparations were published in June 2019. In the updated chapter, USP <795> (last revised in 2014) for nonsterile compounded preparations, the concept “water containing” will be replaced with “water activity.” Water activity determines the susceptibility of a nonsterile preparation to microbial growth and the potential for degradation of the active ingredient because of a chemical reaction induced by the presence of water. This would significantly affect the beyond-use dates and result in a recommendation to add preservatives to certain compounded products (Table 7). Pharmacies are not required to measure “water activity” for the ingredients used in the formulation but should use the tables “Water Activity of Common Compounded Nonsterile Dosage Forms” in USP <795> and “Applications of Water Activity Determination to Nonsterile Pharmaceutical Products” in USP General Chapter <1112> to determine whether their products can be considered aqueous or nonaqueous.
- j. Given the “water activity” of the ingredients in the recipe, the revised USP <795> may recommend adding a preservative to extend the beyond-use date. Given the “water activity,” even preserved formulations cannot be given a beyond-use date past 35 days, even if the formulation was deemed stable for a longer duration (up to 90 days), according to published studies. Adding a preservative to the existing formulation could render it unstable. The preservative chosen must be compatible with all the other ingredients of the formulation and be nonreactive with the container and closure used to dispense the formulation. It is likely that these updates may require that stability studies be repeated with added preservatives to ensure the active ingredient concentration is maintained within 10% (90%–110%) of its original concentration over the 35 days of expiration date.

Table 7. Comparison of Beyond-Use Dates Between Current and Revised USP <795>

Current USP <795> Beyond-Use Dates	Revised USP <795> Beyond-Use Dates
Water-containing oral formulations = 14 days	Nonpreserved aqueous = 14 days
Water-containing topical/dermal and mucosal liquids and semisolid = 30 days	Preserved aqueous = 35 days
Nonaqueous formulations = 6 mo	Nonaqueous dosage forms = 90 days
	Solid dosage forms = 180 days

4. Challenges in using compounded nonsterile extemporaneous formulations:
 - a. Lack of bioavailability, efficacy, and safety data:
 - i. Studies to establish the bioavailability, efficacy, and safety of extemporaneous formulations are generally cost-prohibitive because of lack of funding for conducting the necessary clinical studies.
 - ii. Efficacy and safety data of an extemporaneous formulation obtained in adult studies may not be reproducible in a pediatric population. For example, an extemporaneous suspension of omeprazole in sodium bicarbonate was effective in preventing clinically significant upper GI bleeding and maintaining excellent gastric pH control in critically ill adults. However, a study of mechanically ventilated critically ill pediatric patients receiving the same extemporaneous suspension in recommended standard doses did not show the expected gastric acid suppression. Inadequate amount/volume of bicarbonate used in the smaller pediatric doses was hypothesized to cause this difference in bioavailability and efficacy by failing to protect omeprazole degradation from the acid in the child's stomach.
 - iii. Patients receiving extemporaneous formulations should be monitored to ensure they achieve the expected clinical benefit and have no untoward effects.
 - b. Lack of standardized concentrations for extemporaneously compounded formulations creates a significant risk of medication error for the formulations that have stability and beyond-use dates for several concentrations. Medication errors may occur when:
 - i. Patients or caregivers remember and report drug dose in milliliters. There could be a significant difference in the dose administered depending on the concentration of the oral formulation.
 - ii. Prescriptions are transmitted from one setting to another (from inpatient to outpatient or from one institution to another). A medication error may easily occur if the concentration of the formulation being compounded is not the same at every stage of the transition.
 - c. Standardization of these formulations may significantly decrease medication errors during compounding, dispensing, or administration. The American Society of Health-System Pharmacists has received FDA funding to develop and implement standard concentrations for both the intravenous and oral liquid dosage forms used in all health care settings and across the health care continuum. This initiative, Standardize 4 Safety, lists standardized concentrations for intravenous medications and compounded oral liquids for adult and pediatric patients. To reduce medication errors, health care systems are encouraged to use these lists.
 - d. Cost
 - i. Most pharmacies may lack the technical expertise to undertake new stability studies or repeat them after the USP <795> updates go into effect. Testing for chemical stability involves the use of specific and complex analytic methods. Many analytic tests are not available in the pharmacy or a health care facility; thus, they may need to be outsourced to contract laboratories. A contract laboratory chosen for conducting analytic tests should follow USP General Chapter standards using official methods and techniques for testing. Pharmacies or health care facilities may not have the financial resources to employ external laboratories to conduct these stability studies or equip a laboratory.

- ii. Reimbursement for preparing and dispensing extemporaneous formulations can be difficult. Prior authorizations may be required and can be time-consuming. Reimbursement may not cover all the costs, especially if an active ingredient is only available as an expensive injectable.
- iii. Specialty pharmacies involved in compounding various extemporaneous formulations do not usually accept health insurance and may directly bill the patient for the total cost of the extemporaneous formulations.
- iv. When a commercially manufactured liquid dosage form becomes available, it may be more expensive than the compounded formulation, but pharmacies are legally required to dispense the commercially marketed formulation, if available.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer B is correct. The narrow therapeutic index necessitates individualized dosing and therefore development of a rectal dosage form of several strengths. Answer A is incorrect because avoiding first-pass metabolism by rectal drug absorption predominantly depends on the part of the rectum absorbing the drug. The inferior and middle rectal veins drain the lower part of the rectum into the inferior vena cava and thus directly into the systemic circulation and bypass the liver. Answer C is incorrect; cutting of suppositories for drugs with a narrow therapeutic index may result in an unpredictable dose because uniform distribution of the drug throughout the suppository cannot be guaranteed. Answer D is incorrect. In the absence of a suitable rectal dosage form, oral liquids can be administered rectally. The rectal dosage form would need to be the smallest amount and osmotically balanced to prevent premature evacuation of the bowel and therefore erratic and incomplete delivery of the dose.
2. Answer C is correct because renal function in infants is immature compared with adults, resulting in lower clearance of renally eliminated drugs, including aminoglycosides. Answer A is incorrect because higher V_d and lower clearance contribute to a longer half-life. Answer B is incorrect because the V_d of aminoglycoside is increased in neonates. Answer D is incorrect; although clearance varies in newborns, it is consistently lower than in adults with normal renal function.
3. Answer D is correct. Monitoring a trend in SCr values (increasing SCr with worsening renal function) and urine output (decreasing urine output worsening renal function) over time is the most accurate method of monitoring renal function in children younger than 1 year. Answer A is incorrect because the bedside Schwartz equation has not been validated for children younger than 1 year. Answer B is incorrect; although the original Schwartz equation allowed calculation of eGFR for children younger than 1 year, with the change in SCr assay method to isotope dilution mass spectrometry, the original Schwartz equation is no longer valid. Answer C is incorrect because this method would be invasive (would need a Foley catheter to accurately collect and measure urine over 24 hours) and time-consuming.
4. Answer B is correct because phenytoin is a highly protein (albumin) bound drug; however, the binding capacity of albumin for phenytoin is low in newborns, resulting in higher free phenytoin concentrations with the potential for toxicity. Therefore, monitoring free phenytoin concentrations should be considered. Answer A is incorrect because phenytoin does not displace bilirubin and can be used as anticonvulsant therapy in newborns. Answer C is incorrect because phenobarbital can induce phenytoin metabolism, thus requiring larger phenytoin maintenance doses. Answer D is incorrect; although some *HLA* genotypes have been associated with the development of rash (not hepatotoxicity), this is a rare adverse event in newborns.
5. Answer B is correct. Renal function (GF) reaches adult values by 3 months of age and exceeds them thereafter. Therefore, because of the high renal clearance and short half-life of vancomycin in this population, they require more frequent dosing than do adults. Answer D is incorrect for the same reason. Answer A is incorrect because very little vancomycin is hepatically metabolized. Answer C is incorrect; although there is some binding to plasma proteins, it is less than 50%, and changes in binding need not be considered.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer B is correct. When administered enterally, medication A is absorbed on an empty stomach. However, continuous enteral feeds would not allow for an empty stomach therefore decrease absorption unless the feeds were held for a considerable time around medication administration. Answer A is incorrect because medication A is absorbed well on an empty stomach when the amount of gastric acid in the stomach would normally be highest; therefore, absorption of medication A is aided by an acidic environment. Increased gastric acid production would increase the absorption of medication A. Answer C is incorrect because the stomach is the absorption site for medication A. Decreased gastric emptying time would mean the drug would remain in the stomach for a longer time, which would help absorption. Answer D is incorrect because the site of absorption for medication A is the stomach. Therefore, intestinal emptying time should not significantly affect absorption.
2. Answer B is correct because BSA/weight ratio decreases as a pediatric patient matures from a premature infant to an adult. If the same amount of drug is applied to the skin, the amount of drug absorbed by an infant is larger than in an adult because of the smaller body weight. O.H.'s BSA is 0.082 m^2 , and his BSA/weight ratio is 0.11. E.M.'s BSA is 0.91 m^2 , and her BSA/weight ratio is 0.04. Answer A is incorrect because O.H. has a greater BSA/weight ratio than E.M. Answer C incorrect because E.M. would have a more mature, thicker epidermis and stratum corneum than O.H., thus decreasing transdermal absorption compared with O.H. Answer D is incorrect because O.H. would have a thinner and more immature stratum corneum than E.M. because of his prematurity.
3. Answer D is correct because the percentage of total body fat increases with age as the infant grows. Preterm infants like O.H. have very low body fat compared with children like E.M., who is 8 years of age and will have a second period of body fat increase in the maturational continuum. Answer A is incorrect because the higher the plasma protein concentrations, the larger the V_d values for protein-binding drugs. However, O.H. is a premature neonate compared with E.M.. Neonates have lower total plasma protein concentrations and lower drug-protein-binding capacities, resulting in lower plasma protein binding of various drugs compared with the older population. Thus, neonates will have a smaller V_d than older infants and children. Answer B is incorrect because total body water is higher, not lower, in neonates, especially in premature neonates compared with children. Therefore, they have a larger V_d for hydrophilic drugs. Answer C is incorrect because as the total body water decreases with age, the proportion of total body water as extracellular water also decreases (from around 60% in premature newborns to around 20% in adolescence).
4. Answer C is correct. A.E.'s weight of 76.1 kg is greater than 125% (200%) of his IBW of 37.2 kg. A.E.'s adjusted body weight is 53 kg. Hydrophilic drugs such as gentamicin distribute into extracellular water. However, in pediatric patients with obesity such as A.E., the percentage of extracellular water is relatively lower than their weight. Therefore, an adjusted body weight is used to calculate the dose of drugs with a narrow therapeutic index such as gentamicin. A.E.'s gentamicin dose using his adjusted body weight is $53 \text{ kg} \times 7 \text{ mg/kg/dose} = 371 \text{ mg}$. Therapeutic drug monitoring (TDM) of gentamicin should not be delayed until the third dose (steady state) but should be carried out with the first dose to help estimate V_d and individualize A.E.'s dose, despite not being at steady state. Answer A is incorrect because using IBW may underestimate the percentage of A.E.'s ABW being lean body mass and therefore the percentage of extracellular water. Using IBW may underdose A.E. and cause therapeutic failure. Answer B is incorrect; although the dose is calculated correctly, the TDM of gentamicin should not wait until the third dose but should be carried out with the first dose. Answer D is incorrect; using A.E.'s ABW will overestimate his gentamicin dose and lead to significant toxicity.
5. Answer A is correct because CYP2C9 activity is highest between age 6 months and 3 years (exceeds adult values) and peaks at 3–4 years of age. Therefore, for a drug extensively metabolized by CYP2C9, a higher

- milligram per kilogram dosing may be required. Answer B is incorrect because CYP2C19 activity is the lowest in a premature neonate (32 weeks' GA, 14 days PNA) (fetus – 10% of adult values; neonate – 30% of adult values); therefore, the clearance of a drug extensively metabolized by CYP2C19 will be the slowest. Answer C is incorrect because CYP3A4 activity increases from prematurity to adulthood. It is highest at 1–4 years of age, exceeding adult capacity. Therefore, a drug extensively metabolized by CYP3A4 would have a shorter (shortest) half-life. Answer D is incorrect; development of CYP3A5 activity is independent of maturational age; therefore, the half-lives (and thus elimination rate constants) of drugs extensively metabolized by CYP3A5 may not significantly differ between pediatric and adult populations.
6. Answer B is correct. The eGFR (estimated on the basis of CrCl) for J.D. is $(0.413 \times 119)/1.3 = 37.8$ mL/minute/1.73 m². According to the recommendations for dose adjustments for renal function, J.D.'s dose of piperacillin/tazobactam will be 35–50 mg/kg/dose intravenously every 6 hours. Answer A is incorrect because for his decreased renal function, he needs a dose adjustment. Answer C is incorrect because the dose exceeds the mg/kg/dose recommendation for his renal function, but the dosing is less frequent and can lead to therapeutic failure because piperacillin/tazobactam is responsible for time-dependent killing. Answer D is incorrect because the dose is decreased and the dosing is less frequent, which would be more suited for an eGFR less than 30 mL/minute/1.73 m².
7. Answer C is correct; the phenothiazine class of drugs is contraindicated in children younger than 2 years because of an increased risk of severe respiratory depression. Answer A is incorrect; although fluoroquinolones are documented to damage the cartilage of weight-bearing joints and cause arthropathy in immature animals, use of topical fluoroquinolones is acceptable because the risk is very low. Use of systemic fluoroquinolones is allowed if the benefits outweigh the risks. Answer B is incorrect because the risk of kernicterus and encephalopathy is highest in neonates with an increased incidence of hyperbilirubinemia. Ceftriaxone can displace bilirubin from albumin-binding sites in an infant with hyperbilirubinemia. Displaced bilirubin crosses the immature blood-brain barrier and can be fatal. Answer D is incorrect because among the tetracycline class of drugs, doxycycline does not have the same adverse effects as tetracycline and demeclocycline.
8. Answer A is correct. Patients with the *HLA-B*5701* allele cannot receive abacavir and must be tested for this biomarker before abacavir is initiated. Answer B is incorrect because it is the wrong biomarker; it should be the *HLA-B*1502* allele. Answer C is incorrect because patients who are heterozygous for both TPMT and NUDT15 need a substantial dose reduction (greater than 10%). Answer D is incorrect because use of codeine in CYP2D6 ultra-metabolizers causes rapid and complete conversion to its metabolite morphine. Life-threatening and fatal respiratory depression is a risk in these patients, not lack of pain control. Poor CYP2D6 metabolizers are at risk of lack of pain control upon use of codeine.
9. Answer D is correct. Tacrolimus has stability data for two separate concentrations. Without use of a standardized concentration, this patient is at risk of serious medication error if the concentration compounded at the near-to-home pharmacy is not the same as the concentration compounded at your institution. Answer A is incorrect. Although there are no bioavailability data for this compounded prescription, tacrolimus is therapeutically monitored, and doses are adjusted to achieve serum concentrations with documented efficacy. Answer B is incorrect because compounded formulations of tacrolimus have beyond-use dates confirmed through published stability studies. Answer C is incorrect because a prior authorization has already been obtained at the original institution and will apply irrespective of the transfer of prescription. However, without prior authorization from the insurance company, reimbursement for a compounded formulation is difficult, and the patient may be charged for it.

PRACTICE MANAGEMENT

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Learning Objectives

1. Describe the responsibilities of a pediatric pharmacy representative to the pharmacy and therapeutics committee to ensure appropriate formulary management for the pediatric population.
2. Design a medication use evaluation to evaluate medication use or processes in a pediatric population.
3. Use the American Society of Health-System Pharmacists–Pediatric Pharmacy Association guideline to devise a plan for providing pharmacy services to pediatric patients in a health care system.
4. Develop strategies to manage drug shortages.
5. Devise a plan to optimally use medical and informational technology for pediatric patients.
6. Use appropriate quality improvement methods and metrics to improve the quality of care provided to pediatric patients.

Abbreviations in This Chapter

CHIP	Children's Health Insurance Program
CPOE	Computerized provider order entry
EHR	Electronic health record
MUE	Medication use evaluation
ICU	Intensive care unit
P&T	Pharmacy and therapeutics (committee)
RCA	Root cause analysis
REMS	Risk Evaluation and Mitigation Strategies
VAERS	Vaccine Adverse Event Reporting System

Self-Assessment Questions

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

1. The pharmacy and therapeutics (P&T) committee at a children's hospital is reviewing an application to add an antimicrobial agent that is active against highly resistant gram-negative bacteria and has new data for use in children. There is a desire to add this medication to formulary, but there are concerns about resistance development to this medication, which has occurred in adult populations. Which strategy is best for adding this medication to formulary?
 - A. Maintain the antibiotic as a non-formulary product to discourage use except in emergencies.
 - B. Add the antibiotic to the formulary with no additional restrictions.
 - C. Add the antibiotic to the formulary, but restrict its use in the pediatric intensive care unit (ICU).
 - D. Add the antibiotic to the formulary, but restrict its use to the infectious disease service.
2. Which is most likely to ensure change in practice or processes after completing a medication use evaluation (MUE)?
 - A. Adult and pediatric populations are assessed using the same outcomes.
 - B. A multidisciplinary team of key stakeholders participates.
 - C. High-cost medications are evaluated.
 - D. The scope of the evaluation is expanded once data collection begins.
3. Which best describes inventory practices that should be used during a drug shortage?
 - A. Drug supply should be obtained by any means possible, including "gray market" or compounding sources.
 - B. The decision to use "gray market" or compounding sources should be made before critical supply levels are reached.
 - C. When supply is available, the pharmacists responsible for inventory should order as much as possible, regardless of use history.
 - D. The pharmacy should order alternative non-formulary products before a multidisciplinary review of need for alternatives.
4. An MUE is being undertaken to help ensure that prescribers in the outpatient setting are following the Risk Evaluation and Mitigation Strategies (REMS) for mycophenolate mofetil and pregnancy. Of the following, which step should be taken first?
 - A. Identify the pediatric and adult outpatient areas in which females of childbearing age are prescribed mycophenolate to determine the scope of the evaluation.

- B. Discuss requirements for contraception and pregnancy testing with the family advisory committee to determine how patients and families will best receive education.
 - C. Discuss which outcome measures related to pregnancy test frequency and contraception counseling are most appropriate for this MUE.
 - D. Develop a protocol for pregnancy testing for females of childbearing age to ensure compliance with the REMS program.
5. Which best illustrates a potential barrier faced by a pediatric pharmacist when providing care to pediatric patients?
- A. A formulary diuretic is available both as tablets and as an oral liquid suspension.
 - B. A hospital uses a standardized dosing nomogram for acetaminophen oral liquid suspension.
 - C. A pump for subcutaneous treprostinil cannot accurately deliver the initial starting dose in an infant.
 - D. The safety and efficacy of off-label use of a new sedative in a pediatric ICU patient is supported by an available prospective study.
6. Which strategy can best help ensure the safe provision of pharmacy services for pediatric inpatients?
- A. Dispensing patient-specific dilutions as determined by the Rule of 6.
 - B. Dispensing multidose products, such as a reconstituted bottle of amoxicillin suspension.
 - C. Purchasing products with preservatives like benzyl alcohol, when possible.
 - D. Avoiding the use of high-osmolarity products in peripheral lines.
7. Pediatric pharmacists providing pharmacy services in an outpatient care setting should have an understanding of the unique medication needs of patients and their caregivers. Which would be considered the most essential component in providing outpatient services to pediatric patients and their caregivers?
- A. Educating pediatricians on poison prevention.
 - B. Providing drug information education for nurses and providers.
 - C. Educating caregivers on accurate medication measurement.
 - D. Knowing what medication preparations are commercially available.
8. Which best describes the location and maximum volume that should be used for an intramuscular injection in a neonate?
- A. Deltoid, 0.5 mL.
 - B. Deltoid, 1 mL.
 - C. Vastus lateralis, 0.5 mL.
 - D. Vastus lateralis, 1 mL.
9. Which best describes a challenge faced when adapting adult electronic health records (EHRs) for use in pediatric patients?
- A. Fewer dosage forms and concentrations are needed.
 - B. All products used in pediatric patients have manufacturer barcodes available for scanning.
 - C. Chronological age is appropriate for all patients when designing dosing algorithms.
 - D. Rounding algorithms can cause inappropriate dosing in neonates.
10. As the neonatal intensive care unit clinical pharmacist, you are assisting with the drug library build for a new smart infusion pump that your institution will be using. One upgrade with the new pumps is bidirectional interoperability with the electronic health record. Your Level IV academic medical center is part of a larger health system that includes four community hospitals that also have Level II or III neonatal intensive care units. The community hospitals will begin to use the pumps in a second phase of pump acquisition that will begin 12 months after your go-live date. Which option best describes considerations for standard drug concentrations among your institutions?
- A. A list should be made of all standard drug concentrations used at the various institutions, and all concentrations should be built into the neonatal intensive care unit drug library.
 - B. Each institution should individually build a neonatal intensive care unit drug library based on the standard drug concentrations used at the individual institution.

- C. The institutions should meet to review differences in standard concentrations and harmonize the concentrations used at the institutions.
 - D. The community hospitals should harmonize their standard drug concentrations into one drug library, but your neonatal intensive care unit should maintain its standard concentrations because of specialized needs related to the higher level of care.
11. A joint task force created by the American College of Clinical Pharmacy (ACCP) and the Pediatric Pharmacy Association (PPA) developed strategies to expand the quality and capacity of clinical pharmacy services provided to pediatric patients. Which strategy would best enhance clinical pharmacy services?
- A. Developing minimum expectations for the training of those entering pediatric practice.
 - B. Substituting on-the-job training for postgraduate year two (PGY2) residency experience.
 - C. Expanding the service coverage of currently available clinical pharmacy specialists.
 - D. Developing expectations for the participation of clinical pharmacists in pediatric research.
12. A 12-year-old female patient presents to the primary care clinic for her second human papilloma virus vaccine. After the vaccine, she becomes dizzy and lightheaded and faints; she recovers after a few minutes without any persistent complications. Her parent is wondering about reporting this adverse effect because she has concerns about the overall safety of the human papilloma virus vaccine and was hesitant to give it to her daughter. What is the best response?
- A. These are known vaccine complications and should not be reported to Vaccine Adverse Event Reporting System (VAERS).
 - B. These are known vaccine complications but may be reported to VAERS by the health care team.
 - C. These are known vaccine complications but may be reported to VAERS by the patient's parent.
 - D. These are known vaccine complications but may be reported to VAERS by the patient's parent or the health care team.
13. Which best describes the purpose of the core set established by the Children's Health Insurance Program (CHIP) Reauthorization Act?
- A. To assess the quality of care provided to children by a health system.
 - B. To assess the quality of care provided to children within various private insurance programs.
 - C. To assess the quality of care provided to children within Medicaid/CHIP.
 - D. To assess the quality of care provided to children by community health offices.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

Domain 2: Practice Management and Medication Safety; Task(s): 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7

I. INTRODUCTION

- A. Medication management for pediatric patients is affected by marked anatomic, developmental, and physiologic differences from adults.
- B. Pediatric medication management requires a highly individualized approach to medication therapy.
- C. Published pharmacokinetic, safety, and outcomes data for medications used in the treatment of pediatric patients are often lacking.
- D. Pharmacists may encounter difficulties in the medication use process for pediatric patients because dosage forms and drug delivery devices are often manufactured for use in adult patients.
- E. These challenges require a unique practice management skill set for the pharmacists involved in providing specialty care for pediatric patients in both the inpatient and outpatient settings.
- F. Pediatric pharmacists use in-depth knowledge of developmental pharmacokinetics and pharmacodynamics, together with a specialized subset of practice management skills, to address the unique needs of this patient population. These skills can be used in:
 - 1. Formulary maintenance
 - 2. Development of evidence-based practice guidelines and policies
 - 3. Development, assessment, and optimization of all components of the medication use process to ensure the safe administration of medications to pediatric patients
 - 4. Continuous quality assessment of policies, guidelines, and medication use processes

II. PEDIATRIC CONSIDERATIONS FOR MAINTAINING A FORMULARY AND DEVELOPING MEDICATION USE GUIDELINES OR PROTOCOLS**Patient Case**

1. You are the pediatric pharmacy representative to the P&T committee for a health system that provides care to both pediatric and adult patients. Acid-suppressive therapies are being reviewed as a cost-saving initiative. You receive the formulary monograph for the histamine-2 receptor antagonists to review before the upcoming meeting. The recommendation is to maintain one intravenous and enteral agent for use in all age groups, but no pediatric data or assessments of available dosage forms are included. Which is the best next step to ensure that the recommendation presented in the monograph to the P&T committee is complete and accurate for the pediatric patients cared for by the health system?
 - A. Gather input from key pediatric stakeholders regarding the recommendations for medications from this class that should be placed on the formulary for pediatric patients.
 - B. Identify and evaluate available pediatric pharmacokinetic, safety, and outcomes data for the class of medications to make recommendations for updating the monograph.
 - C. Evaluate the monograph's adult data for applicability and extrapolate to pediatric patients to make recommendations for adding to the monograph.
 - D. Identify the availability of extemporaneous preparations of pediatric-friendly dosage forms for the class of medications to make recommendations for adding to the monograph.

- A. Formulary System and P&T Committee (Am J Health Syst Pharm 2021;78:907-18)
1. Formulary – List of medications and other information representing the clinical judgment of experts in the organization
 - a. List of available medications, medication-associated products, and devices
 - b. Drug information
 - c. Medication use policies/guidelines
 - d. Decision support tools
 2. Formulary system – Organizational process to establish policies for the safe, appropriate, cost-effective use of medications, medication-associated products, and devices.
 - a. Health care facilities and hospitals
 - b. Payers
 3. P&T committee
 - a. Composition: Physicians and other prescribers, pharmacists, nurses, administrators, quality improvement professionals, medication safety leaders, informaticists, patient and family engagement advisors, etc.
 - b. Responsible to the medical staff; organization and authority dictated by medical staff bylaws and other organizational policies
 - c. Administrative needs
 - i. Charter
 - ii. P&T secretary/formulary manager
 - iii. Committee/subcommittee scopes
 - iv. Attendance tracking, quorum definition
 - v. Appeals process
 - vi. Term limits
 - vii. Conflicts of interest reporting process
 - viii. Voting process that ensures transparency
 - (a) Roll call
 - (b) Process to delegate or prohibit delegation of votes.
 - ix. Policies and procedures
 - x. Management of minutes, agendas, records, and communication of decisions
 - d. Responsibilities
 - i. Manage the formulary system
 - ii. MUE process
 - iii. Monitor for adverse drug events
 - iv. Prevent medication errors
 - v. Develop guidelines and policy
 - e. Conflicts of interest
 - i. Should be disclosed by all involved in the formulary process
 - (a) Voting members
 - (b) Those submitting requests to change the formulary
 - ii. Policies should address the involvement of those with conflicts of interest in formulary process.
 4. Management
 - a. Make evidence-based decisions to optimize care
 - b. Consider clinical, ethical, legal, social, philosophical, quality-of-life, safety, and economic concerns
 - c. Review all medications: Complementary/alternative therapies, nonprescription medications, blood factors, contrast media, etc.

- d. All medication use policies should be approved by the P&T committee through a formal review process.
 - i. Policies should describe:
 - (a) Formulary addition/deletion process
 - (b) Conduct of drug class reviews
 - (c) Development, implementation, dissemination, and monitoring of medication-use guidelines
 - (d) The medication use process
 - (1) Procurement of medications/selection of manufacturers
 - (2) Nonformulary medication use
 - (3) Management of radiopharmaceuticals
 - (4) Drug shortage management
 - (5) Use of medication delivery devices
 - (e) Prior authorization/patient access
 - (f) Implementation of P&T decisions into the EHR
 - ii. Review may occur in subcommittees/expert panels
 - iii. P&T Committee should have relationships with other institutional committees with functions that also affect the medication use process
 - iv. Role of industry representatives should be carefully considered and defined
 - (a) Use of samples
 - (b) Funding (direct and indirect)
 - (c) Educational programming
- 5. Evaluation of medications
 - a. Evidence-based evaluation
 - i. Systematic review of the literature
 - ii. Higher-quality evidence (e.g., meta-analysis, randomized controlled trials) should direct decision-making.
 - iii. May need to consider expert opinion and internal/unpublished data
 - iv. Standard monograph should be used to document information considered in the process
 - b. Drug reviews
 - i. New drug monographs – New U.S. Food and Drug Administration (FDA)-approved medication or indication
 - ii. Reevaluations of previous formulary decisions
 - iii. Therapeutic class reviews
 - iv. Expedited review – Newly approved medication with no therapeutic alternative; new safety concerns
 - c. Pharmacoeconomic assessment (Crit Care Clin 2012;28:11-24)
 - i. Models use mathematical equations to analyze value of and rank drug interactions (Expert Opin Pharmacother 2004;5:1867-80).
 - ii. Define perspective of analysis: patient versus institution versus payer, etc.
 - iii. Cost-minimization
 - (a) Considers costs only
 - (b) No consideration of outcomes
 - (c) Appropriate when outcomes are therapeutically equivalent
 - (d) Example: Cost minimization analysis of two treatment regimens for low-risk rhabdomyosarcoma in children where direct medical costs were compared between two regimens that had similar failure-free survival outcomes (Pediatr Blood Cancer 2014;61:970-6).

- iv. Cost-effectiveness analysis
 - (a) Determine option with the lowest cost to achieve a stated outcome
 - (b) Benefits measured in natural units such as life-years, infections avoided, etc.
 - (c) Reported in cost-effectiveness ratio, e.g., dollars per ventilator-free day gained
 - (d) Example: Cost-effectiveness analysis of anesthetic agents during peripheral intravenous cannulation in the pediatric emergency department in which outcome is the cost to reduce 1 unit on visual analog scale for pain (Arch Pediatr Adolescent Med 2008;162:952-61).
- v. Cost-utility evaluation
 - (a) Type of cost-effectiveness analysis
 - (b) Benefits measured in quality-adjusted life-years, combining both morbidity and mortality
 - (c) Allow for comparison among different diseases or outcomes to determine greatest gain for expenditure
 - (d) Example: An analysis comparing the cost per quality-adjusted life-day of different treatment regimens for acute otitis media in children (J Pediatr 2017;189:54.e3-60.e3).
- vi. Cost-benefit analysis
 - (a) Costs and outcomes expressed monetarily
 - (b) Outcome expressed in net gain or loss in dollars
 - (c) Depending on the perspective of the analysis, such as benefit to society, a cost-effective treatment for a rare disease may be deemed to be of lower benefit than a less cost-effective intervention for a more common disease state.
 - (d) Example: Comparison of influenza hospitalization costs versus cost of universal influenza immunization in children age 6 to 23 months (J Pediatr 2005;147:807-11).
- vii. Consider all medication and nonmedication costs:
 - (a) Monitoring
 - (b) Length of stay
 - (c) Personnel
- viii. Analyses from the literature should be evaluated rigorously.
 - (a) Consider the assumptions made in evaluations.
 - (b) Consider a specific institution's costs.
 - (c) Manufacturer information is disposed to bias and should be interpreted cautiously.
- d. Formulary exception process should be available to allow access to needed medications for unique patient needs.
- e. Subformularies may be used for specific patient populations.
- 6. Strategies for managing medication use
 - a. Generic medications
 - i. Financial benefits
 - ii. P&T policy should guide generic substitution, narrow therapeutic range medications, use of branded medications, etc.
 - b. Biosimilars
 - i. Not generically equivalent
 - ii. Implications for coverage and reimbursement models, differences in clinical indications, legal and regulatory restrictions, contractual obligations
 - c. Therapeutic interchange – Gives pharmacists the authority to change from a non-formulary medication to a formulary agent
 - d. Guided-use strategies: Medications added to the formulary with restrictions in place to reduce cost or improve safety
 - i. Established-use criteria: Patients must meet the criteria to receive a medication (e.g., restricting intravenous acetaminophen to patients who cannot receive oral or rectal acetaminophen).

- ii. Restriction to service: Only specific services may order or approve a medication (e.g., only hematology can order or approve the use of blood factor products).
 - iii. Restriction to prescribers with specific training (e.g., restricting agents causing deep sedation to anesthesiologists)
 - iv. Restricting medications to specific areas within the hospital: Requires specialized equipment, training, monitoring (e.g., limiting use of vasopressors to ICUs)
 - v. Requiring the medical director's approval before dispensing; especially appropriate for high-cost non-formulary agents
- e. Clinical practice guidelines
 - i. May be national/international or local
 - ii. Recommended products in guidelines should generally be formulary
 - iii. May be useful in managing expensive specialty therapies, but consider volume of use and resources to guide benefit in developing and maintaining guidelines
- f. Specialty medications
 - i. Establish policies to ensure continuity of care
 - ii. Determine appropriate sourcing of specialty medications.
- g. Medication use evaluation (MUE)
 - i. Establish systematic plan to review, track, and enhance the medication use process
 - ii. MUE may be useful in formulary decision making
 - iii. MUE may be used to review medications after formulary addition and use.
- 7. Off-label use (Am J Health Syst Pharm 2008;65:1272-83)
 - a. Use of a drug outside FDA-approved indications (Clin Pharmacol Ther 2012;91:796-801)
 - i. Outside labeled age range, including preterm neonates or young children
 - ii. Outside labeled weight range
 - iii. No pediatric clinical data
 - iv. Statement that use is contraindicated in children
 - v. Used outside labeled indications
 - vi. Administered by a route not included in labeling
 - vii. Pregnancy (Semin Perinatol 2015;39:523-6)
 - viii. Medication labeling for same product can vary among different countries
 - b. Off-label use in children
 - i. Depending on the population, 18%–65% of prescriptions may be for off-label use.
 - ii. Depending on the population, 42%–100% of pediatric patients receive medications for off-label use.
 - c. Principles of off-label use (Am J Health Syst Pharm 2008;65:1272-83)
 - i. Based on published evidence
 - (a) Comprehensive and balanced
 - (b) Selective use of studies that show benefit without considering the entire body of literature examining the off-label use should be discouraged.
 - ii. Patient safety should be the utmost concern.
 - iii. The P&T committee should establish protocols to direct use if a medication is to be used off-label regularly.
 - iv. Prescriber is ultimately responsible for safety and efficacy.
- 8. Patient safety actions and considerations of the P&T committee
 - a. Look-alike/sound-alike potential and management of risks
 - b. Incorporation of risk evaluation and mitigation strategies (REMS) program compliance
 - c. Proactive risk-assessment projects such as failure modes and effects analysis
 - d. Regular review of medication event data, including near misses

- e. Targeted quality improvement projects
 - f. Promotion of technologies that improve the safety of the medication use system
 - g. Review and dissemination of patient safety information available from other organizations (e.g., Institute for Safe Medication Practices)
 - 9. EHR and the formulary
 - a. EHR should support policy decisions by providing guidance to prescribers at order entry and pharmacists on verification
 - i. Dosing and monitoring
 - ii. Guidelines
 - iii. Guided use strategies
 - b. Establish a standard process to assure integration of formulary decisions across all relevant technologies
 - 10. Drug shortages
 - a. The P&T committee should set the organization's priorities.
 - b. The P&T committee should develop strategies through evidence-based review to effectively address shortages.
 - i. Alternatives
 - ii. Restrictions/rationing
 - c. Communicate decisions with patients and personnel
 - i. Use EHR to convey updated restrictions, prohibit ordering of shortage products, guide use of alternatives, etc.
 - ii. Drug shortages should be regularly discussed by P&T
 - 11. Revenue strategies
 - a. Reimbursement is increasingly complex
 - b. Traditional models
 - i. Fee-for-service
 - ii. Manufacturing contracts
 - iii. Wholesaler agreements
 - iv. Inpatient reimbursement
 - c. Consider effects of the following:
 - i. Payer mix: Medicare, Medicaid, commercial, private
 - ii. 340B Drug Pricing
 - iii. Specialty pharmacy mandates
 - (a) Brown bagging (patient obtains medication from specialty pharmacy and takes to provider for administration)
 - (b) White bagging (specialty pharmacy ships medication to provider for administration to a specific patient)
 - (c) Clear bagging (specialty pharmacy internal to the institution dispenses medication and transports it to site of administration)
 - (d) Determine policy on use or nonuse of medications not supplied by the institution
 - d. High cost medications
 - i. Investigate benefits with finance office
 - ii. Establish process to validate coverage of high-cost products
- B. Pediatric Considerations for Formulary System and P&T Committee
- 1. Pediatric patients should be represented by a pediatric pharmacist on P&T committees (Am J Health Syst Pharm 2018;75:e136-50).
 - a. Pediatric subcommittee should be formed if committee is mostly adult-focused.
 - b. P&T committee decisions should indicate if they apply to pediatric patients.

2. Pediatric pharmacy representation on P&T committees should:
 - a. Ensure that available safety and outcomes data for pediatric patients are included in all monographs
 - b. Ensure that medications used primarily or exclusively in pediatric patients are considered for formulary addition
 - c. Recommend age-specific restrictions for medications that should not be used in pediatric patients (e.g., KIDs List: Developed by Pediatric Pharmacy Association contains medications potentially inappropriate for prescribing in children) (J Pediatr Pharmacol Ther 2020;25:175-91).
 - d. Recommend adding appropriate dosage forms to ensure safe medication use in pediatric patients and minimize the need to alter commercially available products
 - e. Help develop comprehensive plans to communicate and implement formulary changes to minimize the risk of error with practice change, including any changes or additions needed within the hospital or health system information technology

Patient Case

2. You work at a free-standing children's hospital that is part of a health system. There are neonatal intensive care units at several of the community hospitals throughout the health system. As your health system moves to a new electronic medical record, there is a desire to standardize medication use to make the build more efficient. Currently, there are multiple "starter" parenteral nutrition formulas at different institutions for use in newly born preterm infants. A team of multidisciplinary stakeholders has been brought together for a medication use evaluation on how to harmonize the formulas, and through literature review, has determined there is limited evidence to dictate optimal practice. What is the next best step to take?
 - A. Allow each institution to keep separate formulas; because there is limited data to support best practice, no institution should be forced to change.
 - B. Examine the differences between the various formulas, consider any safety, stability, operations, or cost issues, and propose a harmonized formula after stakeholder discussion.
 - C. Follow the free-standing children's hospital practice because this hospital has the most expertise and has the most patients who will be affected by the change.
 - D. Provide education for the reasons for change to all nurses and physicians in the neonatal intensive care unit.

C. Medication Use Evaluation (MUE)

1. Performance improvement method to optimize patient outcomes and improve medication use (Am J Health Syst Pharm 2021;78:168-75).
 - a. Should be interdisciplinary, but pharmacists generally should be responsible to lead, develop, and coordinate the process.
 - b. Objective may be to assess a patient-centered therapeutic outcome or process related to a medication or class of medications.
2. MUE is useful (Pharmacotherapy 2014;34:5S-13S) when:
 - a. Questions exist on a medication's benefit (e.g., off-label use, conflicting or limited evidence)
 - b. Evidence to choose between two or more medications is limited
 - c. Medication use process requires analysis (e.g., prescribing, preparing, dispensing, administering, monitoring)
3. Goals of MUE (Pharmacotherapy 2014;34:5S-13S)
 - a. Evaluate efficacy
 - b. Enhance safety; may include minimizing adverse drug events
 - c. Standardize treatment
 - d. Optimize therapy

- e. Meet the standards of government, regulatory, or professional groups
 - f. Minimize cost
 - g. Assess value of innovative practices (Am J Health Syst Pharm 2021;78:168-75).
4. Medications and processes to prioritize for MUE (Am J Health Syst Pharm 2021;78:168-75)
- a. Medication that causes adverse events or has toxicity at normal doses
 - b. Medication use in a population prone to adverse events
 - c. Significant interactions
 - d. Process or medication used by a large population
 - e. Medication or process is critical
 - f. Medication must be used in a particular way for efficacy
 - g. Change in formulary status proposed
 - h. Medication recalled or withdrawn from market
 - i. Medication used experimentally (not-FDA approved) or off-label
 - j. New or innovative practices
 - k. Expensive medication with unknown cost benefit
 - l. Assess compliance with formulary restrictions
 - m. Evaluation of pharmacist-driven protocols or collaborative practices
 - n. Medication or process identified through analytics tools or safety evaluations
5. Logistical issues (Pharmacotherapy 2014;34:5S-13S)
- a. Need for support structure and organizational authority to ensure completion of MUE and implementation of change on the basis of findings
 - b. Key multidisciplinary stakeholders should be identified and involved in all phases, including designing the MUE, collecting data, disseminating results, and implementing change.
 - c. Multidisciplinary collaboration, definition of responsibilities, and accountability are vital.
 - d. MUEs should include an evaluation of all groups affected by the evaluated medication or process.
 - e. MUEs should ensure that pediatric-specific evaluations do not go unnoticed because of fewer patients and a perception of a smaller impact.
6. MUE process (Pharmacotherapy 2014;34:5S-13S)
- a. Identify the clinical or operational question to study
 - b. Develop the scope of the evaluation
 - i. Consider pediatric age groups
 - ii. Consider pediatric-specific data and the outcomes that should be evaluated
 - c. Collect data
 - i. Establish measurements and end points
 - ii. Objective measures are preferred to subjective measures.
 - iii. Measures should be accessible, relevant, and reproducible.
 - iv. Poor documentation may hinder data collection.
 - d. Analyze the data
 - e. Disseminate the results
 - f. Implement change
 - i. Results of MUE should be actionable and lead to changes in guidelines or practice.
 - ii. Pediatric-specific needs for implementing change should be considered.
 - iii. Education is important, but information systems should also be used to support or automate new practices.
 - iv. Performance should be monitored, and deviations from new practice should be addressed.
 - v. Obtain feedback from MUE team and those affected by change (Am J Health Syst Pharm 2021;78:168-75).
 - vi. Consider publication of results (Am J Health Syst Pharm 2021;78:168-75).

7. Barriers to a successful MUE
 - a. Lack of authority or involvement of medical staff
 - b. Lack of organization and leadership
 - c. Lack of communication within the MUE team or lack of involvement among the team
 - d. Lack of documentation of MUE activities
 - e. Poor data integrity, data not readily available, or amount of time needed for data collection impeding patient care
 - f. Failure to follow through with continuous quality improvement based on results
 - g. Failure to include unique or under-represented patient groups in the scope of the MUE (e.g., pediatrics)
 - h. Lack of dissemination of results, education of changes based on results, and failure to include changes within hard-wired systems

Patient Case

3. At your institution, rituximab is a formulary medication, but it is restricted to use for certain labeled indications. The pediatric nephrology department would like to amend the restriction to allow use to treat frequently relapsing and steroid-dependent nephrotic syndrome. You are assigned to review the literature for consideration for P&T committee formulary addition. Which is most important to include in the literature review?
 - A. A series of three case reports of rituximab use in children who positively benefited from rituximab in this type of nephrotic syndrome.
 - B. A review article that explains the mechanism of action for rituximab in this type of nephrotic syndrome.
 - C. A randomized, placebo-controlled trial of rituximab in 50 children with this type of nephrotic syndrome.
 - D. A randomized, placebo-controlled trial of rituximab in 200 adult patients with this type of nephrotic syndrome.

- D. Medication Use Guidelines and Protocols in Pediatric Patients
 1. Helpful to standardize medication use processes, especially when pediatric data are lacking
 2. Process for medication use guideline development (BMJ 1999;318:593-6; Evid Based Nurs 2005;8:68-72)
 - a. Prioritize areas for developing guidelines
 - i. Practice variation
 - ii. Care costs
 - iii. Gaps in care
 - iv. Institutional practice is not current according to the accepted standards of practice
 - b. Establish a multidisciplinary team
 - i. Involve key stakeholders at initiation and throughout
 - ii. Multidisciplinary group decreases bias.
 - iii. Team leader should have pertinent clinical knowledge but not be biased toward a particular outcome.
 - iv. Pediatric pharmacists have unique skills to evaluate, develop, and safely apply medication use guidelines and protocols and should take an active role in directing guideline and protocol development.
 - c. Establish a guideline development process
 - i. Plan for identifying, summarizing, and analyzing relevant evidence
 - ii. Define the process the group will follow to establish the guideline.
 - d. Identify and analyze the available evidence
 - i. Assess quality
 - ii. Evaluate whether evidence is current

- iii. Include pharmacokinetic, safety, and efficacy data in the specific population (e.g., neonates, adolescents)
- iv. Assess studies for outcomes to guide the design of medication use guidelines or protocols
- v. Lack of data may not preclude the need for medication use guidelines or protocols for the pediatric population.
 - (a) Available pediatric pharmacokinetic and safety data should be used to devise the optimal dosing and monitoring for incorporation into the guideline or protocol.
 - (b) Adult efficacy data may be used to develop a plan for outcomes assessment once the guideline or protocol has been implemented.
 - (c) When pediatric data are unavailable, adult pharmacokinetic, safety, and efficacy data should be evaluated for their relevance and translatability to the pediatric population.
- e. Gather expert opinion if evidence is inconclusive
- f. Develop a guideline or protocol
- g. Seek an external review of the guideline
 - i. Validity of content
 - ii. Clarity
 - iii. Applicability to patient setting
- h. Obtain an official endorsement of the guideline or protocol
 - i. Approval from administrators in areas affected by protocol
 - ii. Approval by the P&T committee (Am J Health Syst Pharm 2021;78:907-18)
- i. Disseminate the guideline or protocol
 - i. Involve key stakeholders in developing appropriate education and implementation plans for their respective discipline
 - ii. Assess the varying educational needs of different disciplines
 - iii. Prepare super-users in the affected departments to answer questions and facilitate associated processes
- j. Schedule a review and revision
 - i. Plan for when and how the guideline/protocol will be reviewed and updated
 - ii. Evaluate guidelines for:
 - (a) Sustainability
 - (1) Evaluate the processes associated with the guideline or protocol for any barriers to completion
 - (2) Failure to address barriers or assess the ongoing use of the guideline or protocol may result in workarounds or a decline in the use of the process after implementation.
 - (b) Safety
 - (1) Vigilantly assess safety to ensure that patients have not been placed at risk by either labeled or off-label uses of medications
 - (2) Especially important when minimal to no safety or efficacy data are available in pediatric patients
 - (3) Unique or uncommon adverse drug effects or risks of error should be reported to add to the body of data in the literature for pediatric patients.
 - (c) Outcomes
 - (1) Should be predefined in the design process
 - (2) Routine evaluation should occur for both internal and external reporting. Reporting of standard medication use processes in pediatric patients can help add to the body of evidence for use in pediatric patients.
- iii. If resources are insufficient to properly review, update, and revise, old guidelines should be retired (Am J Health Syst Pharm 2008;65:1272-83).

3. Considerations when developing pediatric medication use guidelines and protocols:
 - a. Developmental pharmacokinetic changes
 - b. Increased risk of error in the pediatric population
 - c. Logistical issues with medication administration
 - d. Inherent level of difficulty involved in monitoring with both subjective scales (e.g., pain scales) and objective measurements (e.g., amount of blood needed for laboratory values)
4. When appropriate, medication use guidelines and protocols developed for adult patients should consider the potential for use in pediatric patients and should include appropriate safeguards.

III. PROVIDING PEDIATRIC PHARMACY SERVICES IN HOSPITALS AND HEALTH SYSTEMS

Patient Case

4. Because of the weight-based dosing regimens often used in pediatric patients, endless individualized doses can increase the risk of error, impair workflow in the dispensing process, and minimize the ability to use technology such as automated dispensing cabinets. In your daily review of patient medication profiles, you have identified that several prednisolone 3 mg/mL oral suspension individualized doses are being dispensed, many of which may be difficult to accurately measure with the available oral syringes (e.g., 16.1 mg/5.37 mL). Which process would best improve the medication use process for prednisolone 3 mg/mL?
 - A. Develop a standardized dosing nomogram and build it into the computerized provider order entry (CPOE) system such that doses are automatically converted to a limited number of doses.
 - B. Round all doses to either whole or 0.5-mL doses when orders are verified so that prepackaged products of 3 and 1.5 mg can be used for patient-specific doses.
 - C. Educate the order verification pharmacists to contact prescribers to have the doses rounded.
 - D. Educate the medical staff on the concentration of the formulary prednisolone liquid.

- A. Pediatric Considerations in the Medication Use Process (Am J Health Syst Pharm 2018;75:e136-50)
 1. Pediatric patients pose unique challenges in the delivery of pharmacy services for several reasons:
 - a. Lack of published safety and efficacy data
 - b. Lack of commercially available products
 - c. Weight-based dosing
 - d. Complex calculations
 - e. Developmental limitations in communication
 - f. Difficulty implementing standardized systems to meet the special needs of these patients (Am J Health Syst Pharm 1994;51:1690-2)
 2. Practice model
 - a. Depends on scope of services for pediatric patients
 - b. Regardless of model, institutions should strive to meet best practices for pediatric patients.
- B. Personnel Resources
 1. Strategies for expanding the quality and capacity of clinical pharmacy services provided to pediatric patients as devised by the joint opinion group of the ACCP Pediatrics Practice and Research Network and the Pediatric Pharmacy Association (formerly PPAG) (Pharmacotherapy 2013;33:243-51):
 - a. Develop plans to ensure optimal pharmacy services for clinical coverage and staffing in pediatric inpatient and outpatient care areas

- b. Elevate the minimum expectations of those entering pediatric pharmacy practice
 - i. Postgraduate year one (PGY1) in a pediatric hospital or with several pediatric rotations
 - (a) Sufficient training for pediatric staff pharmacist or student preceptor
 - (b) Provides broad experience and enhances understanding of global concepts
 - ii. PGY2 or PGY1 with 3–4 years of clinical experience in pediatric direct patient care
 - (a) Sufficient training for a clinical pharmacist or residency preceptor
 - (b) Builds on the PGY1 foundation
 - (c) Expands pharmacotherapy knowledge base through exposure to many experiences and specialists
 - (d) Programs focus on specialized practice to prepare trainees to enter specialist practice or academic appointment.
 - iii. Board certification
 - (a) Uniform approach to ensure appropriate clinical credentials
 - (b) Essential for those who participate in direct patient care or precept advanced pharmacy practice and residency experiences or have faculty appointment
 - c. Develop a new or expand an existing PGY2, when feasible, to expand the number of qualified pediatric clinical pharmacists
 - d. Sustainable methods for facilitating the involvement of pediatric clinical pharmacists in research:
 - i. Clinical pharmacist participation and support of research efforts is considered a standard of practice (www.accp.com/docs/positions/guidelines/standardsofpractice.pdf).
 - ii. Should maintain competence in a variety of areas, including research
2. Areas of need:
- a. Research to establish the projected number of pharmacists needed to provide direct patient care in the pediatric setting, evaluating:
 - i. Use of health care resources by pediatric patients
 - ii. Recommended ratio of practicing pediatricians to pediatric clinical pharmacists
 - iii. Settings in which pediatric pharmacy practice expertise is needed
 - b. Needs assessment methods to define the optimal number of pediatric operations and clinical pharmacists needed within a health care setting to provide safe and optimal medication-related care to a pediatric population
- C. Pharmacy Operations and Practice (Am J Health Syst Pharm 2018;75:e136-50)
- 1. Pharmacy hours
 - a. 24-hour pediatric pharmacy services should be available, when feasible.
 - b. If 24-hour pediatric pharmacy services are not feasible:
 - i. A pediatric pharmacist should remain available on call
 - ii. Limited inventory of medication should be accessible for urgent use
 - 2. Institutional policies and procedures should include considerations for the care of pediatric patients; ensure pharmacists and others with pediatric expertise are included in the development of institutional policies and procedures.
 - 3. Provision of drug information (Am J Health Syst Pharm 1994;51:1690-2)
 - a. Pediatric pharmacists should have access to pediatric-specific electronic and hard-copy drug information resources when making therapy decisions.
 - b. Data for off-label use of specific medications for pediatric disease states should be evaluated, when available.
 - c. Pediatric pharmacists should actively participate in educating those in other health care disciplines on drug therapy and the medication use process.

4. Medical emergencies (Am J Health Syst Pharm 2018;75:e136-50)
 - a. Pediatric pharmacists should contribute to:
 - i. Organization of code cart and contents
 - ii. Pediatric emergency drug references
 - b. Cardiopulmonary resuscitation, code, and trauma committees and response teams should include a pharmacist.
 - i. Pediatric pharmacists should receive appropriate training and certification in basic and advanced life support (pediatric advanced life support, advanced cardiac life support or neonatal resuscitation as appropriate).
 - ii. Pediatric pharmacists should attend neonatal and pediatric resuscitations.
5. Immunizations (Am J Health Syst Pharm 2018;75:e136-50)
 - a. Pharmacists should contribute to policies and procedures regarding immunizations for patients and employees.
 - b. Pharmacists should provide immunizations when practical and allowed by law.
6. Orientation and continuing professional development programs should be provided for pharmacists who care for pediatric patients, especially because limitations to the number of formally trained pediatric pharmacists may result in the need for on-the-job training (Am J Health Syst Pharm 2018;75:e136-50; Am J Health Syst Pharm 1994;51:1690-2; JPediatr Pharmacol Ther 2021;26:762-66). Core areas for competency should include:
 - a. Dosing
 - i. Weight-based calculations
 - ii. Applicability of standard doses versus dose rounding
 - b. Pediatric fluid calculations and nutrition needs
 - c. Diseases and medications commonly encountered in pediatric patients and pertinent clinical practice guidelines, including common infectious pathogens and empiric antibiotic regimens
 - d. Effects of age- and disease-specific conditions on drug and dosage form selection
 - i. Safety concerns with the medications themselves
 - ii. Risk of exposure to excipients (e.g., benzyl alcohol in neonates)
 - iii. Appropriate routes of administration and volumes
 - iv. Key Potentially Inappropriate Drugs in Pediatrics (KIDs List)
 - e. Preparation
 - f. Administration
 - g. Developmental pharmacokinetics and pharmacodynamics
 - h. Safety culture and risks of medication errors in pediatric patients (Joint Commission 2008;39)
 - i. Reporting medication errors and adverse events (Joint Commission 2008;39)
 - j. Normal vital signs for age
 - k. Normal laboratory values for age
 - l. Appropriate pediatric references
7. Outpatient pharmacy services should have an in-depth understanding of the unique needs of pediatric patients and caregivers, including:
 - a. Dosage forms that may require compounding for appropriate dosing and administration
 - b. Should provide the most appropriate and accurate measuring device upon dispensing
 - c. Medication education should include a detailed discussion of administration and reconstitution, if needed.
 - d. Consider need to provide extra supply for day care, school, etc.

D. Medication Therapy Optimization (Am J Health Syst Pharm 2018;75:e136-50)

1. Clinical pharmacy services
 - a. Prioritize clinical services to provide the highest level of care to the highest-risk populations
 - b. Clinical pharmacy services should include:
 - i. Rounding
 - ii. Monitoring drug therapy
 - iii. Adverse drug event surveillance
 - iv. Patient/family education
 - v. Discharge counseling
 - c. Clinical pharmacy services should be documented, preferably in the electronic medical record.
 - d. Pharmacists should provide direct patient care whenever possible, including under collaborative practice agreements.
 - e. Pharmacists should be responsible for continuity of care related to medication therapy.
 - f. Pharmacists or other designated team members (e.g., trainees, technicians) should obtain or have access to medication histories.
2. Medication preparation
 - a. Compounding
 - i. Commercially available products may not meet the needs of pediatric patients.
 - ii. Train personnel to meet practice standards and applicable regulations.
 - iii. Use standard concentrations and standardized recipes (from referenced sources, whenever possible).
 - iv. Maintain logs of compounded products with lot numbers.
 - b. Sterile preparations
 - i. Parenteral preparation should meet USP 797/USP 800 standards.
 - ii. Sterile compounding outside the pharmacy should be limited to immediate use in emergencies.
 - iii. Pharmacists require knowledge of pediatric fluid requirements, administration techniques, and devices.
 - (a) Need for a limited number of standard concentrations
 - (b) Safe preparation of dilutions
 - (c) Concerns with hyperosmolar solutions
 - (d) Knowledge of excipients
 - c. Unit dose:
 - i. Dispense enteral and parenteral drugs in ready-to-administer forms versus multidose products
 - ii. May require extemporaneous preparation or prepackaging
 - iii. Standardized dosing nomograms can minimize the number of patient-specific dosages and ensure accurate medication measurements.
 - iv. Unit dose packages should have barcodes or radiofrequency identification to support barcode identification during preparation/dispensing and administration and to facilitate inventory management.
3. Medication administration (Am J Health Syst Pharm 2018;75:e136-50)
 - a. Prescribing
 - i. Medication orders for pediatric patients shall include:
 - (a) Allergies
 - (b) Weight (in kilograms) – consider need to use a dosing weight when actual weight is unstable.
 - (c) Weight-based and total doses, when relevant
 - (d) Height, in centimeters
 - ii. Use metric system
 - iii. Avoid non-standard abbreviations

- b. Order review
 - i. Diagnoses and therapeutic purposes of medications should be available to pharmacists.
 - ii. Pediatric-trained pharmacists should prospectively review pediatric orders.
 - c. Pediatric-specific drug administration considerations
 - i. Intravenous
 - (a) Access can be difficult to obtain in neonates/infants.
 - (b) Consider osmolarity limits for total parenteral nutrition.
 - (1) American Society for Parenteral and Enteral Nutrition recommends an osmolarity limit of 900 mOsm/L for peripheral access (J Parenter Enteral Nutr 2014;38:334-77).
 - (2) Many institutions use a higher osmolarity limit to balance the delivery of adequate nutrition, especially to preterm neonates, with risks of central access.
 - ii. Intramuscular (Miller 2017)
 - (a) Injection site
 - (1) Children younger than 3 years: Vastus lateralis preferred
 - (2) Children older than 3 years: Deltoid preferred, vastus lateralis is an alternative
 - (3) Dorsal gluteal region should not be used because of the risk of nerve damage.
 - (4) Ventral gluteal region may be used in older children.
 - (b) Injection volume maximums
 - (1) Small infant – 0.5 mL
 - (2) Older infant/toddler – 1 mL
 - (3) School-aged child – 2 mL
 - (4) Adolescent – 3 mL
 - iii. Intranasal (Pediatrics 2010;126:532-7)
 - (a) Rapid absorption into bloodstream
 - (b) Ideal volume is 0.2–0.3 mL per nostril.
 - (c) Maximum volume is 1 mL per nostril.
 - (d) Mucosal atomizers require overfill to account for dead space volume in the device
 - iv. Intraosseous (Anesth Analg 2010;110:391-401)
 - (a) Provides access to central venous circulation
 - (b) Proximal tibia is the preferred site in infants and children.
 - (c) Sternum, distal femur, medial malleoli, and iliac crest have also been used.
 - (d) All resuscitation medications may be given by the intraosseous route.
 - (e) Administration of some antibiotics (e.g., ceftriaxone, chloramphenicol, tobramycin, and vancomycin) and phenytoin by this route may lead to decreased peak concentrations (Ann Pharmacother 2007;41:1679-86).
- E. Monitoring Medication Use (Am J Health Syst Pharm 2018;75:e136-50)
- 1. Pharmacists should perform proactive assessment of safety and efficacy of medication regimen, reviewing:
 - a. Appropriateness of regimen and dose/route/frequency
 - b. Therapeutic duplication/omission
 - c. Adherence
 - d. Adverse drug reactions and adverse effects – May be more difficult to identify (Am J Health Syst Pharm 1994;51:1690-2)
 - i. Lack of safety data on medication use in pediatric patients
 - ii. Patients unable to communicate because of developmental and/or clinical status
 - e. Allergies
 - f. Interactions

- g. Clinical, laboratory, and physical examination data
 - h. Efficacy of therapy
 - 2. Therapeutic drug monitoring
 - a. Monitor anticoagulants, medications with narrow therapeutic windows or high adverse event rates
 - b. Pediatric pharmacists should have expertise in developmental pharmacokinetics.
 - c. Need for laboratory data should be balanced with the discomfort and risk associated with obtaining blood; send the minimum amount needed for assessment.
 - 3. Education and counseling
 - a. Consider age and education level and need to counsel caregiver versus patient.
 - b. Pharmacists should review written medication education materials developed by others.
 - c. Minimum information:
 - i. Brand and generic name
 - ii. Dosing
 - iii. How to administer
 - iv. Potential adverse drug effects
 - v. Drug interactions
 - vi. Storage, including safe storage for children/preventing accidental ingestion
- F. Evaluating the Medication Use System
 - 1. Documentation of pharmacy services
 - a. Should follow a standard process
 - b. May help support need for further pharmacy services
 - 2. Workload and financial performance
 - a. Consider the full scope of patient care in metrics
 - b. Costs for hospital and system should be included in analysis.
 - 3. Medication safety
 - a. Medication errors are more common in children than in adults.
 - b. Pharmacists should lead medication safety efforts.
 - c. Institutional program to identify, prevent, resolve, and report adverse drug events should be established.
 - d. Pharmacists should be involved in the review of medication errors.
 - e. Other sources should be used to proactively assess for the risk of medication errors (e.g., Joint Commission, Institute for Safe Medication Practices)
 - f. Adverse drug reactions should be reported through MedWatch (<https://www.fda.gov/safety/medwatch/>) to aid in postmarketing surveillance.
 - 4. Antimicrobial stewardship
 - a. Pharmacists should lead development of policies to promote optimal antimicrobial use.
 - b. Pharmacists should monitor culture susceptibilities.
 - c. Pharmacists should encourage prescribing patterns to minimize antimicrobial resistance.
- G. Research (Am J Health Syst Pharm 2018;75:e136-50)
 - 1. Lack of trials to define optimal medication therapy in children
 - 2. Pharmacists should be involved in clinical and practice-based research.
 - a. Institutional review board member
 - b. Primary/co-investigator
 - c. Oversight of investigational drug studies, comparative trials
 - d. Development of policies and procedures related to investigational drugs
 - 3. Know and appropriately apply rules regarding consent/assent procedures in this vulnerable population

4. Pediatric Research Equity Act (<https://www.fda.gov/drugs/development-resources/pediatric-research-equity-act-prea>)
 - a. Authorizes FDA to require pediatric studies for some drugs and biologics
 - b. Goal of studies is pediatric labeling
 5. Best Pharmaceuticals for Children Act (<https://bpca.nichd.nih.gov/Pages/default.aspx>)
 - a. Encourages the pharmaceutical industry to perform pediatric studies to improve labeling for patented drug products used in children by granting an additional 6-month patent exclusivity
 - b. Encourages the NIH to prioritize therapeutic areas and sponsor clinical trials and other research about on- and off-patent drug products that need further study in children
- H. Information Technology–Pediatric Interface
1. Technology should be optimally designed and implemented to standardize all phases of the medication use process.
 - a. Customization may be required because most systems are designed for use in adult patients.
 - b. Pediatric pharmacists should be intimately involved in customizing and implementing technology (Am J Health Syst Pharm 2018;75:e136-50).
 2. Optimizing the EHR for the medication use process in pediatric patients (AHRQ 2015)
 - a. Low rates of EHR adoption in pediatric patients are often the result of poor functionality.
 - b. Breadth of pediatric population may necessitate specific functionalities.
 - c. Medication management
 - i. More complex in pediatric patients
 - (a) Weight-based, individualized dosing and adult dosing both needed
 - (b) More dosage forms than for adults
 - (c) Need for several concentrations and dilutions
 - (d) Use of compounded products
 - (e) Rounding algorithms can contribute to significant dose variation in low-weight patients.
 - (f) Need to account for chronological versus postmenstrual age
 - ii. Decision support
 - (a) Use of CPOE systems alone has not greatly reduced errors, but use of CPOE with clinical decision support has.
 - (b) Advanced strategies are needed to account for the complexity of pediatric care.
 - (c) Significant gap exists between commercially available decision support dosing rules and true clinical practice.
 - (d) Pediatric providers see a higher proportion of inappropriate alerts, increasing overrides and alert fatigue.
 - iii. Optimal system features for electronic prescribing:
 - (a) Should improve safety and efficiency
 - (b) CPOE system should be integrated (or at least interfaced) with the pharmacy's computer system.
 - (c) Weight-based dose calculations and dose-range checking as well as adult dosing
 - (d) Dose rounding to appropriate precision (i.e., measurable doses, in low-weight patients)
 - (e) Display age corrected for gestational age
 - (f) Medications should be available in appropriate forms and concentrations.
 - (g) Create a computer-generated medication administration record and send appropriate orders to a profiled automated dispensing cabinet (J Pediatr Pharmacol Ther 2011;6:427-43)
 - (h) Allow tracking of vaccination history – Ideally from internal and external sources
 - (1) Interface with state registries
 - (2) Share data with other institutions

- d. Enhancing standard, adult-oriented systems is “an intense and sophisticated task and has limitations” (AHRQ 2015).
 - i. Need high level of support and clinician involvement
 - ii. Identify content experts to work with pharmacy operations experts and multidisciplinary colleagues in developing, assessing, and maintaining EHR content for the subspecialty populations
 - iii. Pediatrics is a limited market with low financial gain for commercial vendors (Pediatrics 2004;113:59-63).
- 3. Barcode or radio frequency identification medication administration systems may help prevent medication administration errors, but this can present challenges in pediatric patients (Am J Health Syst Pharm 2018;75:e136-50).
 - a. Obstacles in nursing workflows lead to workarounds.
 - b. Barcode armbands are not optimal for all patients (e.g., swaddled neonate, size of preterm neonates).
 - c. Although adult dosage forms are often available from the manufacturer with barcodes, pediatric formulations are not.
- 4. Smart infusion pumps (ISMP 2020):
 - a. Improve the safety of intravenous medication administration but do not eliminate error
 - i. Programming errors
 - ii. Secondary infusion errors
 - iii. Infusion line or channel mix-up
 - iv. Failure to discontinue an infusion when ordered
 - v. Inconsistent delivery due to low rates
 - vi. Bidirectional interoperability with electronic medical record can further reduce potential of errors.
 - b. Provide data that can help optimize the use of safe practices
 - c. Before implementation, hospital administration must assess the readiness of the technological and physical infrastructure and work to educate staff.
 - i. Smart pump use should be a standard expectation in all care areas (ambulatory, perioperative, etc.) for all medications and IV fluids
 - ii. Pumps should default to a dose-error reduction system and organizational goal should be to use dose-error reduction system at least 95% of the time for both medications and intravenous fluids. Address barriers to achieve the goal of 95% utilization.
 - iii. Only buy or lease pumps capable of wireless updates and bidirectional communication with the EHR.
 - iv. Use tracking location technology.
 - v. Assign responsibility and develop workflow for pump oversight.
 - vi. Ensure adequate resources for pump maintenance.
 - vii. Conduct risk assessment prior to pump implementation.
 - viii. Develop policies and procedures related to transfer of patients using smart pumps, borrowing/renting pumps, and cleaning/maintenance.
 - ix. Implement training and competency standards.
 - x. Report adverse events and communicate with pump users regarding risks and errors.
 - d. Drug library
 - i. Interdisciplinary effort by pharmacy, nursing, and medical staff, biomedical engineering, data analyst, medication safety, and information systems personnel.
 - ii. Standardize communication of drug library content changes to users.
 - iii. Standardize libraries across a health system (also optimizes ability to have bidirectional interoperability).
 - iv. Develop a formal process for change requests and require an independent double-check of each entry prior to go-live.

- v. Tailor care profiles to specific patient populations and acuity (e.g., neonatal ICU)
- vi. Standardize nomenclature as much as possible, including tallman lettering, dose-rate labels, and definitions for administration terms.
- vii. Limit use of volumetric flow rate.
- viii. Standardize and limit medication concentrations with commercially available concentrations as the basis for the library build.
- ix. Restrict use of manual/wildcard/custom concentrations.
- x. Standardize overfill, priming, and flushing programming and procedures.
- xi. Build clinical alerts into library.
- xii. Does not replace independent double-check for high-risk drugs
- xiii. Can be difficult to optimally design for pediatric patients because of both weight-based and non-weight-based dosing for various weight groups
- e. Drug administration limits
 - i. May be “soft” (can be overridden) or “hard” (cannot be overridden)
 - ii. Consider institutional practice, data on internal errors, and limited available data when setting limits.
 - iii. Hard stops should be specifically targeted
 - (a) Difficult to establish
 - (b) Inappropriate hard stops lead to workarounds.
 - (c) Carefully consider the risk of having hard stops versus not having them, and use them deliberately.
 - iv. Be aware of excessive alerts and alert fatigue; regularly evaluate and revise alert settings on the basis of institutional data.
 - v. Educate staff on the purpose of hard and soft alerts.
- f. Continuous quality improvement
 - i. Analyze and review at least quarterly.
 - ii. Use internal and external safety event data.
 - iii. Establish organizational baselines for metrics related to pump use.
 - iv. Implement changes to address any problematic trends identified.
- g. Bidirectional interoperability
 - i. Bidirectional interoperability with the EHR should be implemented with adequate multidisciplinary planning and financial/personnel resources.
 - ii. Expectation should be for autoprogramming for at least 95% of medication and intravenous fluid infusions in all areas
 - iii. Adequate wireless network resources are vital and should be assessed prior to implementation.
 - iv. Standardize names, dosing units, and concentrations, across all technologies and policies/procedures.
 - v. Significant workflow development and testing needed prior to implementation
- I. Management of Drug Shortages (Am J Health Syst Pharm 2018;75:1742-50)
 - 1. Drug shortages can compromise patient safety.
 - a. Changes in ordering, preparing, and dispensing medications
 - b. Use of less-familiar substitutes and/or agents with increased risk of adverse effects or decreased efficacy
 - c. Shortage of drug-related products used in preparation or dispensing (e.g., syringes, evacuated bags, atomizers) can also lead to disruptions in patient care

2. Factors contributing to drug shortages
 - a. Market issues: Prescription medications not subject to supply and demand laws
 - b. Manufacturing and quality problems
 - i. Cause of most shortages
 - ii. Lack of transparency regarding quality of manufacturers under current FDA system
 - c. Production delays and capacity issues
 - i. May be a result of quality issues
 - ii. Generic drugs are especially vulnerable because of a lack of redundancy in manufacturing systems.
 - d. Manufacturer business decisions
 - e. Raw material shortages
 - f. Restricted distribution/allocation
 - g. Inventory practices
 - i. Just-in-time inventory management is used across the drug distribution system to increase cost efficiency, but this increases unexpected shortages at various levels of the supply chain.
 - ii. Stockpiling/hoarding
 - h. Natural disasters
3. Planning for drug shortages
 - a. Drug shortages team: Interdisciplinary team that has access to necessary information and can make decisions related to drug shortages
 - i. Gather and monitor data related to drug product shortages
 - ii. Purchase alternative products
 - iii. Modify procedures for storage, preparation, and dispensing
 - iv. Make conservation and rationing decisions
 - v. Modify information technology systems
 - vi. Communicate drug shortages
 - b. Resource allocation committee
 - i. Should oversee all decisions related to the allocation of scarce products
 - ii. Pharmacist, nurses, physicians, social workers, patient representatives, and ethicists should be involved.
 - iii. May need input from specific departments related to therapeutic use of shortage medications
 - iv. Committee should carefully determine prioritization of medications within a predetermined, standardized ethics framework.
 - c. A formal process to approve alternative therapies is necessary.
 - d. Ethical considerations for drug shortage management process:
 - i. Details should be transparent and publicly available.
 - ii. Process should be applicable to a variety of situations.
 - iii. An appeals process should be available to contest decisions.
 - iv. The process for drug shortage management should be mandatory.
 - v. The affected patient population or the reputation of a clinician should not influence the process.
4. Managing drug shortages
 - a. Identify the drug shortage and assess its impact.
 - i. Operations assessment by pharmacy department
 - (a) Conduct concurrently with therapeutic assessment
 - (b) Investigate the details and expected duration of shortage by contacting manufacturers, distributors, the Centers for Disease Control and Prevention, or the FDA or using the American Society of Health-System Pharmacists drug shortages website (www.ashp.org/drug-shortages).
 - (c) Identify the inventory on hand, including in-floor stock, code carts, and prepared trays.

- (d) Establish the availability of the drug from alternative sources, including compounded sources from trusted compounding pharmacies.
 - (e) Determine historical use by purchasing history as well as actual use data.
 - (f) Assess how long the current supply will last.
 - (g) Assess the inventory of alternative products identified by concurrent therapeutic assessment, and explore their availability from wholesalers/manufacturers.
 - ii. Therapeutic assessment by multidisciplinary team:
 - (a) Conduct concurrently with operations assessment.
 - (b) Determine which patient populations will be most affected by the shortage and patient prioritization within the aforementioned ethical framework.
 - (c) Identify therapeutic alternatives for affected patients.
 - (1) Lack of data regarding use of alternatives in pediatric patients can present challenges.
 - (2) Pediatric patients may be more susceptible to the effects of some drug shortages when no therapeutic alternatives exist (e.g., need for calcium and phosphate for healthy bone development in preterm neonates).
- b. Analyze impact of shortage.
 - i. Determine the impact of alternatives on patient safety and the medication use process.
 - (a) Differences in therapeutic effects when using alternative medications
 - (b) Changes in ordering
 - (c) Changes in medication preparation and distribution
 - (d) Differences in drug administration
 - (e) Need to delay procedures or refer patients to other facilities
 - ii. Financial impact
 - (a) Cost of alternative drug products that may be more expensive, outside of purchasing contracts, or from secondary distributors
 - (b) Personnel costs to manage drug shortage and implement system changes
- c. Develop final action plan.
 - i. Conservation strategies
 - (a) Inventory centralization
 - (b) Par adjustments
 - (c) Repackaging
 - (d) Extended beyond-use dating (with FDA and manufacturer approval or by USP 797-compliant process)
 - (e) Intravenous-to-oral conversions
 - (f) Discontinuation of therapy when not essential
 - (g) Restrict to evidence-based indications
 - (h) Use of alternative strengths or sizes of products
 - (i) Batching
 - (j) Rounding to vial sizes
 - ii. Rationing
 - iii. Plan for changes in information technology systems
 - iv. Determining the roles of those involved in managing shortages
- d. Communicate clearly to all involved parties:
 - i. Medical and front-line professional staff
 - ii. Administrators
 - iii. Pharmacy staff
 - iv. Disclose to patients when shortages delay or impair care.
 - v. Work with public affairs officers to determine appropriate media communication.

- e. Inventory changes
 - i. Refrain from hoarding/stockpiling supply.
 - (a) Worsens shortages by increasing demand above the manufacturer's supply capabilities
 - (b) Ethically problematic because it may prevent patients at other health systems from receiving necessary care
 - (c) Maintaining an increased inventory can have an adverse financial impact on the institution, especially if the product expires before use.
 - ii. Plans for using or not using supply from nontraditional "gray market" or compounding sources or performing in-house compounding should be determined before this is the only option.

IV. IMPROVING THE QUALITY OF MEDICATION MANAGEMENT SERVICES PROVIDED TO PEDIATRIC PATIENTS

Patient Case

5. You have been asked to participate in a quality assessment group charged with improving child Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) scores at your freestanding children's hospital. Which best depicts the projects that pharmacists could participate in to target child HCAHPS scores?

- A. Encourage the use of e-prescribing to decrease the wait time for families at the pharmacy.
- B. Provide discharge counseling focused on medication administration and adverse events.
- C. Increase the presence of pediatric ICU pharmacists on multidisciplinary rounds.
- D. Involve pharmacists in medication allergy assessments at hospital admission.

- A. A unilateral approach to pediatric quality assessment is complicated by the heterogeneity of the pediatric population (Pediatrics 2014;113:199-209).
 - 1. Consider the characteristics of this population:
 - a. Developmental changes
 - b. Dependency on others
 - c. Epidemiology that varies from the adult population
 - d. Risk of poverty
 - e. Racial/ethnic disparities
 - 2. Quality assurance: Adult versus pediatric
 - a. Adult: In general, focuses on wellness in chronic conditions by minimizing the need for acute care for exacerbations
 - b. Many pediatric patients require acute care that has minimal association with chronic conditions.
 - c. Focusing on chronic conditions may not be as useful for a global pediatric population.
- B. Children's Health Insurance Program (CHIP) Reauthorization Act (Acad Pediatr 2014;14(5 suppl):S19-S26):
 - 1. Provided resources to develop pediatric quality measures and standardized measure reporting with the goal of improving health care and outcomes for children
 - 2. Among other actions, the CHIP Reauthorization Act provided:
 - a. Initial child core set of quality measures
 - i. Voluntary use by state Medicaid/CHIP
 - ii. Required annual updates

- b. Pediatric Quality Measures Program (PQMP)
 - i. Established publicly available, evidence-based quality measures for Medicaid/CHIP
 - ii. Improved the child core set
 - iii. Agency for Healthcare Research and Quality and Centers for Medicare & Medicaid Services (CMS) are responsible for achieving PQMP goals.
- C. Updated Core Set for 2022 (www.medicaid.gov/medicaid/quality-of-care/downloads/2014-childrens-report-to-congress.pdf; <https://www.medicaid.gov/medicaid/quality-of-care/downloads/medicaid-and-chip-child-core-set-manual.pdf>; <https://www.medicaid.gov/medicaid/quality-of-care/downloads/core-set-history-table.pdf>)
 1. Pharmacy-related measures can be found in Table 1.
 2. Goals of core measures:
 - a. Making care safer through reducing harm
 - b. Engaging the patient and caregivers as partners in care
 - c. Providing effective communication and coordination of care
 - d. Using effective prevention and treatment practices for leading causes of mortality (i.e., cardiovascular disease)
 - e. Promoting broad use of best practices to enable healthy living within communities
 - f. Improving the affordability of quality care to individuals, families, employers, and governments through new health care delivery models
 3. When applicable, quality programs assessing the care of pediatric patients should align with these national priorities.
- D. Family experience with care either globally or in relationship with a specific encounter—Child Hospital Consumer Assessment of Healthcare Providers and Systems (Child HCAHPS) survey. Pharmacy-related questions:
 1. Parent asked about child's prescribed medication
 2. Parent asked about vitamin, herbal, and over-the-counter medications
 3. Providers explain how to administer new medications after discharge.
 4. Providers explain adverse effects of new medications to be taken after discharge.

Table 1. Core Set of Children's Healthcare Quality Measures 2022 with Applicability to Medication Management Services

Measure	Brief Description
Childhood immunization status	Percentage of children who turned 2 yr of age and received specified vaccines by 2 yr of age (four diphtheria, tetanus, and acellular pertussis; three polio; one measles, mumps, and rubella; three <i>Haemophilus influenzae</i> type b; three hepatitis B; one chickenpox; four pneumococcal conjugate; one hepatitis A; two or three rotavirus; and two influenza vaccines)
Immunization status in adolescents	Percentage of adolescents who turned 13 yr of age and received the specified vaccines by 13 yr of age (one tetanus diphtheria toxoids and acellular pertussis, one meningitis, and three human papillomavirus vaccines)
Asthma medication ratio	Percentage of patients 5–18 yr of age with persistent asthma who had a ratio of controller medications to total asthma medications of ≥ 0.5 during the measurement year

Table 1. Core Set of Children's Healthcare Quality Measures 2022 with Applicability to Medication Management Services (*continued*)

Measure	Brief Description
Metabolic monitoring of children and adolescents receiving antipsychotics	Percentage of children and adolescents 1–17 yr of age who had at least two antipsychotic medication dispensing events of the same or different medication and were monitored for the development of abnormal cholesterol and blood glucose concentrations, which are adverse effects of these medications
Use of first-line psychosocial care for children and adolescents receiving antipsychotics	Percentage of children and adolescents 1–17 yr of age with a new prescription for antipsychotics, who had documentation of psychosocial care as first-line treatment
Follow-up care for children prescribed ADHD medications	Percentage of children with new prescriptions for ADHD medications with three follow-up visits within 10 mo, one of which must be within 30 days of initial dispensing of medication
Contraceptive care – postpartum	Percentage of women 15–20 yr of age who had a live birth and were provided a most or moderately effective method of contraception within 3–60 days of delivery
Contraceptive care –most and moderately effective methods	Percentage of women 15–20 yr of age at risk of unintended pregnancy who are provided a most or moderately effective method of FDA-approved contraception
Consumer Assessment of Healthcare Providers and Systems® CAHPS 5.0H (Child Version Including Medicaid and Children with Chronic Conditions Supplemental Items)	Assessment of caregiver experiences with child's health care provision. Separate questionnaire for caregivers of children with chronic conditions (83-question survey) and of children without chronic conditions (48-question survey) used by Medicaid and CHIP for state reporting

ADHD = attention-deficit/hyperactivity disorder.

Information from: Center for Medicaid and CHIP Services and Centers for Medicare & Medicaid Services. Core Set of Children's Health Care Quality Measures for Medicaid and CHIP (Child Core Set) Technical Specifications and Resource Manual for Federal Fiscal Year 2022 Reporting. March 2022. Available at: <https://www.medicare.gov/medicaid/quality-of-care/downloads/medicaid-and-chip-child-core-set-manual.pdf?t=1653338305>.

E. Role of the pharmacist in:

1. Preventive health care

- Advocacy of routine childhood vaccination
- Promotion of healthy community living through education to prevent tobacco, drug, and alcohol use in adolescents
- Education on injury prevention
- Pregnancy prevention in adolescent females through education and provision of contraception, including emergency contraception, and prescribing contraception when allowed by law
- Promotion of sexual health through education on abstinence and barrier contraception for adolescents

2. Obesity prevention

- Almost 20% of children and adolescents have obesity.
- Risk of adverse health outcomes because of increased weight
- Pharmacists can participate in obesity-reduction strategies through involvement in screenings and educating children, adolescents, and their caregivers on healthy eating and activities.

3. Maternal and infant health – Educating parents on the importance of standards of care to prevent subsequent illnesses in infancy and childhood
 - a. Routine vaccinations
 - b. Vitamin K at birth
 4. Pharmacists are critical members of the team developing evidence-based medication therapy for pediatric patients and should participate in providing medication management services for the patient and caregiver.
 - a. The EPSDT (Early and Periodic Screening, Diagnostic, and Treatment) benefit
 - b. Behavioral health
 - c. Medical homes
- F. Vaccine Adverse Event Reporting System (<https://vaers.hhs.gov/about.html>; Vaccine 2015;33:4398-405)
1. Post-licensure safety monitoring of FDA-approved vaccines
 - a. May uncover adverse events not identified in trials as more patients are vaccinated
 - b. As vaccines are generally administered as preventative care to healthy people, and vaccines may be required by schools and employers, vaccine safety and monitoring are important policy considerations.
 2. Passive reporting system that takes submission from health care providers, manufacturers, and the public
 - a. Vaccine adverse events are temporally associated with vaccines but may be caused by vaccine or coincidental
 - b. Can detect safety signals useful for hypothesis-generating research
 3. Objectives
 - a. Detect new, unusual, or rare events.
 - b. Monitor increases in known adverse events.
 - c. Identify patient risk factors for particular types of adverse events.
 - d. Assess the safety of newly licensed vaccines.
 - e. Detect and address possible reporting clusters.
 - f. Recognize administration errors and safe-use issues.
 - g. Provide a national safety monitoring system for the entire population in response to public health emergencies like pandemics.
 4. Operations
 - a. Reports submitted by mail or on <https://vaers.hhs.gov/reportevent.html>
 - b. Reports coded by contractors
 - c. Reports from public receive acknowledgment and request for follow-up
 - d. Contractor requests medical records, death certificates, etc., for serious reports
 - e. Data analyzed
 - i. Descriptive analysis, historical comparison, and trends over time
 - ii. Disproportionality analysis assesses disproportional reporting of specific events with specific vaccines in comparison to other vaccines.
 - iii. Clinical review of serious reports or reports identified via other forms of analysis
 5. Strengths and limitations
 - a. Diverse reporters
 - b. Real-time reports
 - c. Transparent, publicly available data
 - d. Prone to reporting bias, especially underreporting
 - e. No unvaccinated comparison group
 - f. Public may misconceive causality of reported events

- G. Root cause analysis (psnet.ahrq.gov/primer/root-cause-analysis)
1. Structured methodology to analyze serious safety events
 2. Mandated by The Joint Commission since 1997 to analyze sentinel events
 3. Systems approach to identify both active errors occurring at the interface between people and systems and latent errors, occult problems in the system that lead to errors
 4. Steps of root cause analysis
 - a. Data collection
 - i. Event reconstruction
 - ii. Participant interviews
 - iii. Record review
 - b. Analyze sequence of events
 - c. Identify how event occurred (active errors)
 - d. Identify why event occurred (latent errors)
 - e. Identify factors leading to latent errors
 - i. Institutional/regulatory factors
 - ii. Organizational/management factors
 - iii. Workplace environment factors
 - iv. Team environment factors
 - v. Staffing factors
 - vi. Task-related errors
 - vii. Patient characteristics
 - f. Identify ways to eliminate latent errors and contributing factors in order to prevent the error from occurring again.
 - i. Common failure to implement sustainable solutions
 - ii. Do not rely on education, enforcing existing policies, or other weak solutions.
 - iii. Focus on corrective actions and risk reduction.
 - iv. Measure outcomes related to changes.

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Measuring the Quality of Medication Management Services Provided to Pediatric Patients

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Institutions that provide care for pediatric patients must consider this population in formulary decision making. During monograph development, the available data in pediatric patients must be considered. The best first step is to evaluate the available pharmacokinetic, safety, and outcomes data for the recommended medication and any additional medications in the class (Answer B is correct). For the recommended medication, pediatric pharmacists should determine whether there are age groups in which use of the medication has not been evaluated and compare the breadth of data with that of other medications in the class. Although each of the other processes may be used in formulary review, none would be the next best step. Adult data should be extrapolated only in the absence of pediatric-specific data, not as an initial means of formulating recommendations (Answer C is incorrect). Input from key stakeholders is important once data evaluation has occurred to ensure that the questions of other health care providers are addressed and increase the likelihood that recommendations are well received (Answer A is incorrect). Obtaining the input of key stakeholders before data review may result in bias of formulary decision because of clinician preference and/or experience. Formulation of available products is an important consideration in the formulary management for medications that will be used in pediatric patients. Although extemporaneous preparations may be used when no commercially available product can be identified within a class of medications or potentially when the medication with the best data is unavailable in pediatric-friendly dosage forms, they should not be a primary consideration for recommending adding a medication to the formulary (Answer D is incorrect).

2. Answer: B

During medication use evaluations you may find that specific data to answer questions about pharmacotherapy in pediatric patients are lacking. However, other factors such as safety, operations, and cost issues should also be considered in the evaluation and may help guide decision making (Answer B is correct). Although each institution could be allowed to use separate formulas, there are efficiencies in not building multiple records into the electronic medical record and any other affected technologies (Answer A is incorrect). Although the free-standing children's hospital may have the largest

volume of patients, it is still important to examine its practice in an unbiased manner and consider any safety, operations, or cost issues that may occur by expanding the practice from this institution to other hospitals (Answer C is incorrect). Although it will be important to provide education to nurses and physicians regarding the changes, it is preferred to provide education on the rationale for changes with education about the changes being made (Answer D is incorrect).

3. Answer: C

Off-label medication use is very common in pediatric patients. When off-label medications are to be used, use for the given patient and indication should be supported by the literature. A comprehensive, balanced review of the literature should be done in order to make decisions regarding off-label use, and patient safety should be of utmost concern. Of all the data described earlier, it is most important to include the data that best reflect the population in which you would like to use the medication. If a randomized, placebo-controlled study of pediatric patients is available to describe the off-label use of a medication, this should be included in the decision-making process (Answer C is correct). Without this type of data, adult data can be used to justify the use for a given indication, especially if safety and dosing information are available for a given medication. Thus, you may want to include a randomized controlled trial of a large adult population in your review, but it should be used to support the data in the pediatric trial (Answer D is incorrect). Case series and reports help guide off-label use, but they lack rigorous methodology and safety and efficacy outcomes data and are prone to publication bias. If more robust data are available, use of case series and reports should be minimized (Answer A is incorrect). A review article explaining the proposed mechanism of action for this medication is useful background information for this proposal and should be included, but this is not the most important data to be used in making this decision (Answer B is incorrect).

4. Answer: A

The most effective way to improve this process would be to implement a standard dosing nomogram (Answer A is correct), preferably one that automatically updates doses through the CPOE system to the appropriate standard dose at the point of order entry. Educating order

verification staff and medical staff to use appropriate doses according to the concentration of the preferred agent may be helpful, but these are not hardwired process changes, and the effects from them may wane over time (Answers C and D are incorrect). Dose rounding is useful to ensure that dispensed doses of liquid medications can accurately be measured. However, prepackaging several dosing units to dispense specific doses can be error prone and may use an unneeded number of resources with respect to syringes. In addition, it would be ideal to have dose rounding occur automatically, not as part of the verification process (Answer B is incorrect).

5. Answer: B

Child HCAHPS score items that affect pharmacists are primarily related to the following: obtaining an accurate medication history (including prescription, nonprescription, and complementary medications), ensuring that families know how to administer new medications at home, and ensuring families know what adverse effects they should monitor for with new medications. Thus, pharmacist-provided discharge counseling that focuses on how to administer new medications and the adverse effects of new medications may lead to improved child HCAHPS scores (Answer B is correct). Increasing e-prescribing, increasing pharmacist presence on rounds in the critical care setting, and involving pharmacists in allergy assessment would not be expected to affect caregivers' assessment of these items (Answers A, C, and D are incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS**1. Answer: D**

When there is a desire to add a medication to formulary but concerns about the safety of allowing all prescribers to use the medication, restricting the use of the medication in some way can be helpful (Answer B is incorrect). To prevent resistance to this antibiotic, it should only be used in select patients who cannot receive other therapies. Thus, restricting the use of the medication to the infectious disease service, which has particular knowledge of alternative therapies and the role of this antimicrobial, would be appropriate (Answer D is correct). Restricting the medication to a particular area, such as the pediatric ICU, could lead to inappropriate use or prevent patients who need the medication from receiving it (Answer C is incorrect). If the medication were non-formulary, use would probably be reduced, but the medication would not be built into various technologies such as CPOE, barcode scanning, and syringe pumps. This could lead to safety concerns with use of the medication and delays in therapy (Answer A is incorrect).

2. Answer: B

Medication use evaluations are most effective when a multidisciplinary team of key stakeholders is involved from developing the plan through disseminating the results because this leads to buy-in from all members of the team and helps ensure that concerns from all involved in the medication use process are addressed (Answer B is correct). Scope and outcomes of the MUE should be determined before data collection (Answer D is incorrect). However, outcomes for adult and pediatric populations may vary, depending on the medication to be evaluated (Answer A is incorrect). Although high-cost medications may be evaluated, other considerations (e.g., safety risk and compliance with protocols) should also be used to identify medications and medication use processes for evaluation (Answer C is incorrect).

3. Answer: B

Health systems should have strategies for managing drug shortages. Although the “gray market” and compounding pharmacies may be options for obtaining additional inventory, they are not without potential problems. “Gray market” sources usually have limited supplies of medications, which may be of uncertain quality or unknown sources. Compounded products have been associated with patient harm and death

because of contamination. Thus, health systems should have strategies for using these sources before critical supply levels are reached (Answer B is correct; Answer A is incorrect). Although it is tempting to stockpile or hoard shortage medications when they are available, this can lead to further market disruption and prevent patients at other institutions from receiving necessary care (Answer C is incorrect). Although non-formulary alternatives may be needed, the pharmacy should not order them until a multidisciplinary group determines their appropriateness and reviews the safety concerns related to their use (Answer D is incorrect).

4. Answer: A

When beginning any MUE, the first step should always be to define the scope of the evaluation. This is an important step to ensure that all affected by the medication or process being evaluated are included and considered in the MUE design (Answer A is correct). Once the scope is established, outcomes measures can be defined (Answer C is incorrect). Once outcomes data are available, a protocol can be established to ensure compliance with requirements (Answer D is incorrect). When developing patient education tools, it can be helpful to discuss them with a patient and family advisory committee, but this should not be the initial step of the MUE (Answer B is incorrect).

5. Answer: C

Technologies originally designed for use in adult patients may present challenges when use is attempted in pediatric patients (Answer C is correct). Availability of products in both solid and liquid enteral dosage forms and standard medication-dosing regimens facilitates the care of pediatric patients (Answers A and B are incorrect). Although skill is required to interpret data regarding the off-label use of medications in pediatric patients, a lack of data is generally a barrier to patient care (Answer D is incorrect).

6. Answer: D

Avoiding the use of high-osmolarity products in peripheral lines is especially important in pediatric patients because they often have smaller-gauge intravenous lines in smaller vessels than adult patients and are at increased risk of infiltration and extravasation. Establishing osmolarity limits for peripheral parenteral nutrition and

categorizing medication concentrations as “central line only” are strategies that can be used (Answer D is correct). Preparation of standard medication concentrations by standard recipes is the standard of care for pediatric patients and is required by the Joint Commission. Dispensing patient-specific dilutions as determined by the Rule of 6 can lead to medication errors because of the need for complex calculations and the inability to use standard concentrations in smart pump libraries. Although the Rule of 6 was once commonly used, it should no longer be used (Answer A is incorrect). Optimal practice is to dispense pediatric medications as unit doses so that nurses do not have to manipulate products at the point of administration. Dispensing multidose products should be avoided (Answer B is incorrect). Preservatives like benzyl alcohol and other excipients can cause adverse reactions in pediatric patients, especially neonates and infants (Answer C is incorrect). Hospitals caring for pediatric patients should review formulary dosage forms for the presence of excipients and determine whether they are present in amounts that could lead to patient harm. If possible, products that do not contain potentially harmful excipients should be purchased.

7. Answer: C

Although each of these options would be included in providing pediatric outpatient pharmacy services, in-depth medication education for caregivers that focuses on the accurate measurement of medications is the most essential component to provide caregivers and patients (Answer C is correct). Knowledge of commercially available products is important in providing care but, without appropriate education of the caregivers, will not ensure adequate care to patients (Answer D is incorrect). Providing drug information to nurses and providers and educating providers on poison prevention will affect the care provided to pediatric patients in the outpatient setting; however, this would not be considered the most essential component to provide patients and their caregivers (Answers A and B are incorrect).

8. Answer: C

When administering intramuscular injections to pediatric patients, it is important to know the optimal location for injection as well as the maximum volume that should be injected. For neonates, the preferred location is the vastus lateralis, and the maximum volume that should be injected is 0.5 mL (Answer C is correct; Answers A, B, and D are incorrect). The deltoid should not be used

in neonates (Answers A and B are incorrect). A volume of 1 mL is too large for neonatal intramuscular administration (Answers B and D are incorrect).

9. Answer: D

Using an EHR that was designed for use in adult patients can present challenges in pediatric patients. Pediatric patients require more dosage form and dilution options than adult patients, making the build more complex (Answer A is incorrect). Because compounded products are often used in pediatric patients, barcoding is difficult and may require the generation of barcodes for compounded products (Answer B is incorrect). In neonates, dosing off a postmenstrual age may be more appropriate than dosing off a chronological age, which can make dosing algorithms more complex (Answer C is incorrect). In addition, rounding algorithms can lead to significant dose variation in low-weight patients, leading to inappropriate dosing (Answer D is correct).

10. Answer: C

Bidirectional interoperability of smart infusion pumps with the EHR provides significant safety advantages and can eliminate many types of errors. However, building the pump drug library can be an intensive undertaking. Additionally, it is important that all medication names, dosing units, and concentrations be standardized across all technologies and policies to support interoperability. In order to streamline operations, it is ideal that these elements be standardized across the health system as well. This will allow for efficiencies in development of the drug library and in implementing interoperability with the EHR. Thus, Answer C is the best answer because it will allow for the processes used at the initial institution to be expanded across the other neonatal intensive care units in the health system. Answers B and D would require additional resources to implement interoperability via different processes, decreasing efficiency and increasing costs of both implementation and maintenance and are incorrect. Answer A might result in an excess number of concentrations for each drug which could be difficult to build into the drug library and could also lead to increase in dosing errors.

11. Answer: A

Developing minimum expectations for pharmacists entering pediatric practice to include PGY1 training for operations pharmacists and PGY2 training for clinical specialists should be part of the plan to expand

clinical pharmacy services (Answer A is correct). It is difficult to meet the learning experiences obtained during residency training through on-the-job training or experience, and replacing PGY2 training with this type of experience is not a suitable strategy for expanding clinical pharmacy services (Answer B is incorrect). Adding responsibilities to those that the current clinical pharmacy specialist already has without redistributing services or protecting time can diminish the clinical services (Answer C is incorrect). Participating in research certainly may be a service of clinical pharmacy, though this is more likely to be a result of implementing expectations for training to enter practice than the best strategy to enhance service (Answer D is incorrect).

12. Answer: D

VAERS provides post-licensure surveillance for vaccine adverse events. VAERS provides passive surveillance. Anyone may report to VAERS, including patients or caregivers, health care professionals, and vaccine manufacturers. Any vaccine adverse event may be reported to VAERS, whether or not causality is known. The objectives of VAERS include monitoring reporting trends that may reflect increases in known adverse events, identifying risk factors for particular types of adverse events, detecting reporting clusters for adverse events, and detecting safe-use problems. Thus, it is appropriate to report any serious vaccine adverse events whether or not they are known vaccine complications. Therefore, it is appropriate to report known vaccine complications to VAERS (Answer A is incorrect). Because anyone may report to VAERS, either the health care team or the patient's parent, Answer D is the best response. Answers B and C are not incorrect but are less complete than Answer D.

13. Answer: C

The 2022 core set is designed to assess the quality of care for children who are enrolled in Medicaid and CHIP (Answer C is correct). Although these metrics may be used by other entities such as health systems, private insurance companies, and community health offices to measure quality, they are not required to use these metrics (Answers A, B, and D are incorrect).

TOXICOLOGY

ANTHONY JAWORSKI, PHARM.D., BCCCP

**THE POISON CONTROL CENTER AT THE CHILDREN'S HOSPITAL
OF PHILADELPHIA
PHILADELPHIA, PENNSYLVANIA**

TOXICOLOGY

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**THE POISON CONTROL CENTER AT THE CHILDREN'S HOSPITAL
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PHILADELPHIA, PENNSYLVANIA**

Learning Objectives

1. Describe the U.S. poison control system structure and the common pediatric poisonings reported.
2. Identify the common toxidrome classifications.
3. Review the modalities of gastric decontamination and their role in the present-day management of poison ingestion.
4. Describe the pathophysiology and management of select poisonings.
5. Understand potential management strategies for various substance use disorders.

Abbreviations in This Chapter

ED	Emergency department
HRIG	Human rabies immune globulin
NAPQI	<i>N</i> -acetyl- <i>p</i> -benzoquinone imine
UFH	Unfractionated heparin
WBI	Whole bowel irrigation

Self-Assessment Questions

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

1. E.K. is a 2-year-old boy who was found with an empty bottle of 100-count chewable multivitamins. Each tablet contained 18 mg of iron. He is asymptomatic at the time of presentation at the emergency department (ED). Which method of gastrointestinal (GI) decontamination would be most appropriate for E.K.?
 - A. Give activated charcoal.
 - B. Give multidose activated charcoal.
 - C. Give whole bowel irrigation (WBI).
 - D. GI decontamination is not indicated.
2. J.L. is a 15-year-old female adolescent who presents at the ED with dilated pupils, a heart rate of 140 beats/minute, dry mucus membranes, and urinary retention. Which type of ingestion is she most likely presenting with?
 - A. Opioid.
 - B. Anticholinergic.
 - C. Sympathomimetic.
 - D. Cholinergic.
3. Which is the most common reason for exposures of pediatric patients younger than 6 years reported to U.S. poison control centers?
 - A. Intentional malicious (e.g., Munchausen by proxy).
 - B. Unintentional therapeutic errors (e.g., wrong dose administered).
 - C. Intentional suicide.
 - D. Exploratory ingestions.
4. Which agent would most warrant observation in a hospital after ingestion by a 2-year-old?
 - A. Glyburide 1.25 mg.
 - B. Acetaminophen 325 mg.
 - C. Furosemide 20 mg.
 - D. Metformin 500 mg.
5. K.Y. is a 16-year-old male adolescent found to be minimally responsive at home. An empty bottle of metoprolol tartrate 100-mg tablets was found next to him. He presented at the ED with the following vital signs: heart rate 35 beats/minute, blood pressure 60/32 mm Hg, and respiratory rate 20 breaths/minute. On arrival at the ED, he became unresponsive with no cough or gag reflex. Which is the most appropriate first step in K.Y.'s care?
 - A. Administration of calcium chloride.
 - B. Initiation of a glucagon infusion.
 - C. Intubation and mechanical ventilation.
 - D. Administration of an insulin bolus.
6. C.J. is a 2-year-old boy with persistent nausea and vomiting, hypotension, malaise, and a serum iron concentration of 700 mcg/dL. His mother is concerned that he may have ingested several of her iron pills. Which order for deferoxamine would be most appropriate for C.J.?
 - A. Give deferoxamine 15 mg/kg intravenous bolus x 1 dose.
 - B. Give deferoxamine 15 mg/kg/hour continuous subcutaneous infusion.
 - C. Deferoxamine is inappropriate because his concentration is not toxic.
 - D. Give deferoxamine 15 mg/kg/hour continuous infusion.

7. Which is most accurately considered a toxic blood concentration of acetaminophen after an acute ingestion?
- A. 200 mcg/mL at 2 hours after ingestion.
 - B. 230 mcg/mL at 4 hours after ingestion.
 - C. 9 mcg/mL at 12 hours after ingestion.
 - D. 90 mcg/mL at 4 hours after ingestion.
8. R.O. is a 5-year-old boy who presents at the ED with a wound on his right arm after being bitten by a raccoon while playing in his backyard. The raccoon could not be captured. Which is the most appropriate management strategy?
- A. Give no intervention and monitor for development of rabies symptoms.
 - B. Administer human rabies immune globulin (HRIG) 20 units/kg directly to wound site and human rabies vaccine on days 0, 3, 7, and 14 after exposure.
 - C. Administer HRIG 20 units/kg intramuscularly x 1 and on days 3, 7, and 14 after exposure.
 - D. Administer rabies vaccine at days 7 and 14 after exposure.
9. Which of the following is not an essential function of U.S. poison control centers?
- A. Providing a 24/7 poison helpline.
 - B. Performing laboratory testing for poisonings.
 - C. Reducing unnecessary ED visits.
 - D. Providing patient-specific recommendations to emergency medicine providers.
10. Which most accurately describes the medication that is approved for managing opioid use disorder in patients 16 years and older?
- A. Bupropion.
 - B. Naloxone.
 - C. Buprenorphine.
 - D. Clonidine.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.2, 1.3, 1.4, 1.5, 1.9
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.5
3. Domain 3: Information Management, Research, and Education; Task(s): 3.2, 3.4
4. Domain 4: Public Health and Patient Advocacy; Task(s): 4.3

I. TOXICOLOGY

A. Poison Control Center Overview

1. There are currently 55 accredited U.S. poison control centers, which:
 - a. Provide first aid home management for poisonings
 - b. Save health care dollars by reducing unnecessary ED visits
 - c. Prevent poisoning exposures by increasing awareness in the community
 - d. Assist health care professionals in treating poisoned patients
 - e. Educate health care professionals on toxicology and the diagnosis and treatment of poisoned patients
2. All certified poison control centers submit data to the National Poison Data System (NPDS).
 - a. 2.1 million human exposures were reported to the NPDS in 2020. 42% were in children younger than 6 years, 14% were in the 6- to 19-year-old age group, and 44% were in adults older than 19 years. Table 1 lists the most common substances associated with exposures reported to U.S. poison control centers.

Table 1. Top 10 Substances in Pediatric and Adult Exposures in 2019

Age < 6 Yr	Age > 19 Yr
Cosmetic/personal care products	Analgesics
Cleaning substances	Sedatives/hypnotics/antipsychotics
Analgesics	Cleaning substances
Foreign bodies/toys/miscellaneous	Antidepressants
Dietary supplements/herbals/homeopathic	Cardiovascular substances
Vitamins	Alcohols
Topical preparations	Anticonvulsants
Antihistamines	Cosmetics/personal care products
Pesticides	Antihistamines
Plants	Pesticides

- b. There were 1434 poison-related fatalities in 2020.
 - i. 1.5% of the fatalities were in children younger than 6 years. Although children represent the largest number of exposures, the nature of their exposures (typically exploratory ingestions of small quantities) makes the exposures less likely to lead to serious harm or death.
 - ii. Box 1 shows the agents most often associated with poison-related fatalities for all age groups. The reason for fatal exposures is more likely to be intentional in nature (abuse, misuse, and attempts of suicide).
 - iii. Substances involved in pediatric deaths differ quite drastically and include analgesics, fumes (i.e., carbon monoxide), cardiovascular drugs, batteries, and chemicals.

Box 1. Top 10 Substances Associated with Fatalities in 2020 (all ages)

Miscellaneous sedatives/hypnotics/ antipsychotics
Pharmaceutical and illegal opioids
Acetaminophen alone
Miscellaneous alcohols
Miscellaneous stimulants and street drugs
Calcium channel blockers
β -Blockers
Miscellaneous antidepressants
Selective serotonin reuptake inhibitors (SSRIs)
Acetaminophen combinations

B. Legislative Changes

1. Poison Prevention Packaging Act (PPPA), 1970
 - a. Requires child-resistant packaging for many over-the-counter and prescription medications and hazardous household products
 - b. It has been effective at reducing poison-related fatalities in children. In the first 20 years after PPPA enactment, poison-related deaths decreased from 2 to 0.5 per 100,000 in children younger than 5 years. In the early 1970s, there were more than 200 poison-related pediatric deaths per year; in 2020, there were 74 deaths.
2. The Consumer Product Safety Commission administers and enforces federal safety codes, including the PPPA. Safety reports and National Poison Data System data are often used for legislative changes and advocacy efforts for packaging modifications; for example:
 - a. Topical imidazoline derivatives: Any product containing 0.08 mg or more of an imidazoline (tetrahydrozoline, naphazoline, oxymetazoline, or xylometazoline) in a single package must be packaged in child-resistant packaging (CPSC 2012).
 - b. Hydrocarbons (e.g., tiki-torch fuel): Low-viscosity hydrocarbons must be in child-resistant packaging. In addition to the PPPA, a petition for opaque containers must be submitted; though not officially passed in legislation, many large torch fuel companies have voluntarily changed their products to a dark green or black solution so that they do not resemble apple juice (CPSC 2013: <https://law.resource.org/pub/us/cfr/regulations.gov.docket.14/astm.cpsc.minutes/astm.f15.02.20130827.pdf>).

C. Pediatric Poisonings

1. Infants (younger than 1 year) represent 5% of all exposures.
 - a. Unintentional therapeutic errors can also occur in this population because of inadvertent double administrations from several caregivers, confusion of medication (e.g., oxymetazoline instead of saline spray), and inappropriate measuring of doses (e.g., 10-fold dosing errors as result of missing the decimal place for amounts less than 1 mL).
 - b. Inherently low risk because they are not yet ambulatory
 - c. Consider potential child abuse if an exploratory ingestion scenario is described in a nonmobile infant, especially in those with underdeveloped pincer grasp movement.
2. Toddlers and young children (1–5 years) account for almost half of all poisoning exposures.
 - a. These children are very curious and are constantly exploring their environment.
 - b. They have hand-to-mouth and imitative behaviors, increasing their risk of exposure.

3. Exposure cases are similar between children (6–12 years) and teens (13–19 years). Reason for exposure in preadolescents and adolescents is more likely to be intentional (e.g., abuse, misuse, suicide attempts).
4. As mentioned before, most pediatric exploratory ingestions do not result in harm; however, some medications and substances may cause significant toxicity, even in small amounts (Table 2).

Table 2. Common Medications Harmful to Children in One or Two Dosage Forms^a

Medication Class	Select Examples
Antiarrhythmic Agents	
Class IA	Quinidine, procainamide
Class IC	Flecainide, propafenone
Class III	Amiodarone
Other	Digoxin
Antihypertensive Agents	
α 2-Agonists	Clonidine
β -Blockers	Atenolol, metoprolol, propranolol
Calcium channel blockers	Amlodipine, diltiazem, nifedipine, verapamil
Antidepressant Agents	
Tricyclic antidepressants	Amitriptyline, desipramine, imipramine
Oral Antidiabetic Agents	
Sulfonylureas	Glipizide, glyburide
GI Agents	
Antidiarrheals	Lomotil
Analgesics and Opioids	
Opioids	Buprenorphine, fentanyl, hydrocodone, oxycodone, methadone
Salicylates	Aspirin, oil of wintergreen (methyl salicylate)

^aPlease note: This list highlights some of the most commonly prescribed medications and does not include all medications and substances that can be harmful to children in small amounts.

D. General Toxicology

1. *Toxidromes* is a term combining *toxic* and *syndromes*.
 - a. A classification system to determine the substances probably involved in the poisoning of a patient, given his or her clinical findings
 - b. Can be used as a guide, but a full medical history, history of present illness, physical examination, and laboratory test results are critical in assessing a patient exposed to toxins (Table 3).

Table 3. Common Toxidromes

Toxidrome	Sympathomimetics	Anticholinergics	Cholinergics	Theophylline	β-Adrenergic Blockers	Calcium Channel Blockers	Digoxin
Examples Mental status* Heart rate Blood pressure Temperature Respirations Pupil size Bowel sounds Skin Other	Cocaine, Methamphetamine A, D, P, S, T ↑ ↑ ↑ — ↑ (reactive) ↑ sweaty	Benzotropine, Datura C, D, P ↑ ↑ ↑ — ↑ (sluggish) ↓ flushed/dry	Organophosphates C, D, F, S ↓ (↑) — (↑) — ↑, bronchorrhea ↓ ↑ sweaty “S.L.U.D.G.E.” ¹	A, S, T ↑ ↓ — — (↑) — — vomiting	Metoprolol —, C, (S) ↓ ↓ (—) — — — — hypoglycemia, AV block	Verapamil, Nifedipine —, C ↓ (—) ↓ — — — — vomiting, dysrhythmia	
Toxidrome	Opioids/Clonidine	Barbiturates/ Benzodiazepines	Antipsychotics	Anticonvulsants	Cyclic Antidepressants	Lithium	Dissociatives
Examples Mental status* Heart rate Blood pressure Temperature Respirations Pupil size Bowel sounds Skin Other	C ↓ ↓ ↓ ↓ ↓ ↓↓ ↓ — pale	C ↓ (—) — (↓) ↓ — (↓) — — — bullae	Phenothiazines C, S — (↑) — (↓) ↑/↓ — — (↓) — dry dystonia, NMS ²	Carbamazepine, Phenytoin C, S ↑/↓ — — (↑) — ↓ — ataxia/nystagmus	Imipramine C, S ↑ ↓ (—) — — — (↑) — (↓) dry dysrhythmia	C, D, T — (↓) — — (↑) — — — ataxia, ↑ reflexes, vomiting	PCP, Ketamine A, C, D, P, S ↑ — (↑) — (↑) — — (↓) — sweaty nystagmus
Toxidrome	Iron	Hypoglycemics	Salicylates	Withdrawal	LEGEND		
Examples Mental status* Heart rate Blood pressure Temperature Respirations Pupil size Bowel sounds Skin Other	C ↑ ↓ — — (↑) — — (↑) — vomiting, diarrhea, acidosis	Sulfonylureas C, S ↑ — ↓ — — (↑) — sweaty hypoglycemia	A, C, D, S ↑ (—) — ↑ ↑ — sweaty hypoglycemia, acidosis	EtOH, Benzos A, D, S, T ↑ ↑ — (↑) — (↑) — (↑) ↑ piloerection vomiting, diarrhea	*A = agitation C = somnolence/coma D = delirium F = fasciculations P = psychosis S = seizure T = tremor 1 = S.L.U.D.G.E. (Salivation, Lacrimation, Urination, Defecation, Gastric Cramping, Emesis) 2 = NMS (Neuroleptic Malignant Syndrome) 0 = Less commonly seen, or secondary, effect		

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2. General treatment of poisoned patients: Poisoned patients are treated similarly to any other patient requiring emergency care. The ABCs (airway, breathing, and circulation) are the top priority, and “supportive care” (management of the ABCs) is often the treatment modality used. Afterward, measures are taken to decontaminate the patient, and specific antidotes are given for treatment. However, antidotes are not available for all poisons, supportive care is sometimes inadequate, and further interventions must be used after consulting with a toxicologist.
 - a. Airway: Gag and cough reflex
 - b. Breathing
 - i. Respiratory rate
 - ii. Blood gas
 - c. Circulation
 - i. Heart rate
 - ii. Blood pressure
 - iii. Electrocardiogram
 - d. Altered neurologic status
 - i. Coma or stupor
 - ii. Agitation
 - iii. Seizure
 - e. Management of poisoning
 - i. Supportive care (e.g., intravenous fluids, vasopressors, intubation, and mechanical intervention)
 - ii. Decontamination (e.g., removal of contaminated clothing, gastric decontamination using activated charcoal)
 - iii. Antidotes
 - iv. Enhanced elimination (e.g., dialysis)
3. Gastric decontamination: Use of gastric decontamination measures in the treatment of poisoned patients has decreased tremendously over the past 20 years. Typically, all measures in the text that follows are avoided if the patient has a compromised, unprotected airway (e.g., absent gag or altered mental status and not intubated) because almost all have an associated risk of aspiration.
 - a. Single-dose activated charcoal
 - i. Role in managing poisoning cases:
 - (a) Consider in asymptomatic patients who present within 1 hour after ingesting a potentially toxic dose of a substance.
 - (b) Was administered in almost 8% of all exposures in 1995, compared with less than 2% in 2020
 - (c) Serious adverse events (e.g., aspiration, death) have resulted in decreased use.
 - (d) Formulations containing a cathartic such as sorbitol are not often recommended because of the risk of dehydration and electrolyte imbalance (e.g., children younger than 1 year).
 - ii. Mechanism of action: Adsorbs toxins while in stomach to lessen the extent of absorption; should use within 1 hour after ingestion. Does not adsorb all materials; for example, iron, lithium, and alcohols are unlikely to be adsorbed
 - iii. Adverse effects: Vomiting, constipation, aspiration
 - b. Multidose activated charcoal
 - i. Role in managing poisoning cases:
 - (a) Facilitates adsorption of toxins that undergo extensive enterohepatic recirculation
 - (b) Carbamazepine, dapsone, phenobarbital, quinine, and theophylline have all shown enhanced elimination in volunteer studies.
 - (c) Clinical benefit may not correlate.

- ii. Mechanism of action: Adsorbing toxins to decrease absorption or reabsorption as in enterohepatic recirculation
- iii. Adverse effects: Vomiting, constipation, aspiration
- c. Whole bowel irrigation (WBI)
 - i. Role in managing poisoning cases: May be considered in exposures to long-acting substances, body stuffers or packers, fentanyl patch ingestions, and ingestion of agents not well adsorbed by charcoal. Do not use in patients with absent bowel sounds.
 - ii. Mechanism of action: Concentrated polyethylene glycol with electrolytes decreases GI transit time by producing osmotic-induced diarrhea. Rate of administration is more aggressive than with standard cleanout for colonoscopy.
 - iii. Adverse effects: GI discomfort, diarrhea, aspiration, colonic perforation
- d. Gastric lavage
 - i. Role in managing poisoning cases: May be considered in patients who present less than 1–2 hours after ingestion, who are already intubated, and who have ingested a toxin that may result in significant toxicity for which there is no safe and effective antidote. The invasiveness of this procedure and the lack of consistent evidence supporting its efficacy have led to a very limited number of gastric lavage attempts per year.
 - ii. Mechanism of action: Removal of toxins by flushing saline into the stomach and then removing stomach contents through a large-bore orogastric tube (adults 36–40 French; children 22–28 French). This method cannot remove larger pills or objects.
 - iii. Adverse effects: Esophageal injury, airway trauma, electrolyte disturbances, hypoxia
- e. Syrup of ipecac
 - i. Role in managing poisoning cases: As of 2003, the American Academy of Pediatrics no longer recommends routine use of ipecac in managing ingestions of a potentially poisonous substance. Because of decreased demands, syrup of ipecac is no longer manufactured.

Patient Case

Questions 1 and 2 pertain to the following case.

C.Y. is an 8-month-old boy who presents to the ED with episodes of severe irritability. His vital signs are heart rate 170 beats/minute, blood pressure 60/45 mm Hg, respiratory rate 30 breaths/minute, and temperature 39°C (102.2°F). His mucous membranes are dry, and he has decreased bowel sounds. Blood culture and cerebrospinal fluid tests are negative. A reactive respiratory panel is positive for rhinovirus. He has no significant medical history. C.Y. is receiving no prescription medications, but after further questioning, his mother admits giving him several doses of a liquid over-the-counter medication for a cold in the past 48 hours.

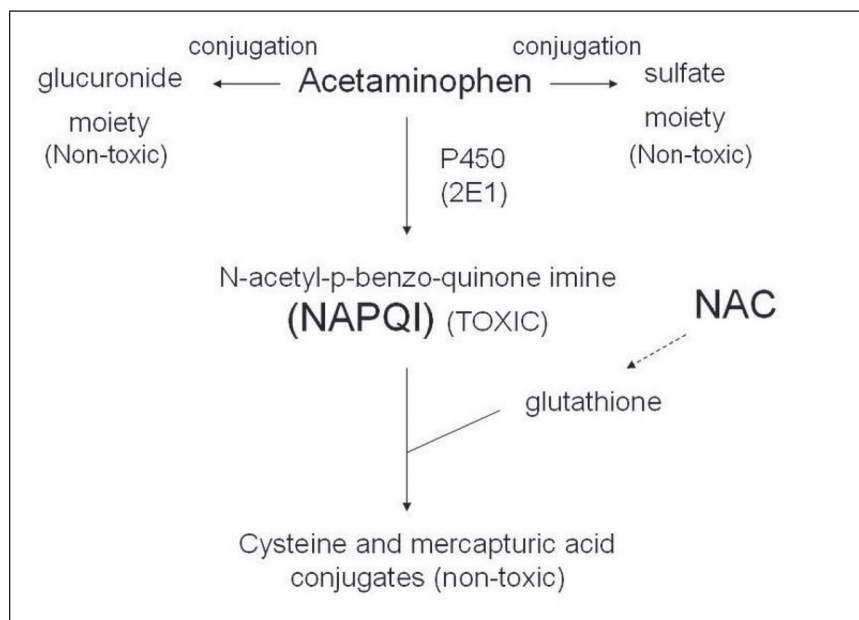
1. Which medication is most likely responsible for C.Y.'s clinical presentation?
 - A. Acetaminophen.
 - B. Diphenhydramine.
 - C. Ibuprofen.
 - D. No medications; presentation is consistent with a rhinovirus infection.

Patient Case (continued)

2. If C.Y.'s symptoms were associated with medication exposure, which gastric decontamination measure would best be considered?
 - A. Give gastric lavage.
 - B. Give single-dose activated charcoal.
 - C. Give WBI.
 - D. No gastric decontamination measures are warranted.

E. Management of Select Agents

1. All cases of suspected self-harm or malicious administration of any substance should be referred to a hospital for evaluation, regardless of substance or exposure amount. In addition, such patients should have routine toxicology screening (e.g., urine drug screen, alcohol, serum acetaminophen, and salicylate concentration if clinical symptoms suggest potential salicylate overdose) because history is often unreliable.
2. Acetaminophen
 - a. Epidemiology: Acetaminophen is a widely used over-the-counter analgesic and is in the analgesic class that is among the top 10 reported exposures to poison control centers. Despite the availability of an antidote, it is also one of the top 10 substances involved in poison-related deaths.
 - b. Mechanism of toxicity: Acetaminophen is metabolized by three pathways: 90% sulfation and glucuronidation and 5% by cytochrome P450 (CYP) 2E1 to *N*-acetyl-*p*-benzoquinone imine (NAPQI) (Figure 1). Less than 5% is renally excreted unchanged.
 - i. NAPQI is a toxic metabolite that binds to hepatocytes, leading to cell death.
 - ii. NAPQI is deactivated by glutathione.
 - iii. In an overdose, glutathione stores become depleted, and NAPQI builds up.

**Figure 1.** Acetaminophen metabolism.

NAC = acetylcysteine.

- c. Signs and symptoms of toxicity
 - i. 0–12 hours: Nausea, emesis, right upper quadrant abdominal pain
 - ii. 12–24 hours: Hepatotoxicity (AST greater than 1000 U/L)
 - iii. 3–4 days: Fulminant liver failure, encephalopathy, coagulopathy, coma, death
 - iv. 7 days: Recovery in survivors
- d. Management
 - i. Acute ingestions (at once or over a 24-hour period) exceeding 200 mg/kg or 10 g (whichever is lower) or chronic ingestions (48 hours or more) of 150 mg/kg/day or 6 g/day x 2 days, whichever is a lesser amount, require hospital management. Situations for which the amount is not known need to be referred as well.
 - ii. Obtain a 4-hour serum acetaminophen concentration, liver function tests (LFTs), prothrombin time (PT) and international normalized ratio (INR), basic metabolic panel (BMP), and lactate (for severe overdoses).
 - iii. Plot concentrations on the Rumack-Matthew nomogram (Figure 2) to determine whether acetylcysteine is indicated. Initiate acetylcysteine therapy if 4-hour concentration is 150 mcg/mL or greater.
 - (a) See Select Antidotes section for more information.
 - (b) For chronic toxicity or unknown time of ingestion, consider empiric acetylcysteine therapy until LFTs and acetaminophen laboratory test results have returned and are reassuring. Chronic ingestions greater than 200 mg/kg within 24 hours, greater than 150 mg/kg/day for 2 days, or more than 100 mg/kg/day for greater than 3 days are particularly at risk of hepatotoxicity.
 - (c) Acetylcysteine is available in two forms: intravenous and oral (the oral formulation is the inhaled form given by mouth). There is essentially no difference in efficacy between the two forms, but the poor palatability and extended treatment time (72 vs. 21 hours) have caused the oral form to fall out of favor.
 - iv. Dosing (see Select Antidotes section)
- e. Management pearls:
 - i. Acetylcysteine is most beneficial to the patient when initiated 8–10 hours after acetaminophen ingestion.
 - ii. Acetylcysteine should still be initiated if a patient presents after 10 hours and the serum acetaminophen concentration is above the treatment-line (Figure 2).
 - iii. There have been cases of delayed acetaminophen absorption after coingestants that slow GI transit (e.g., diphenhydramine, opioids); a careful history and physical examination may help determine which cases need to be followed more closely as a result.
 - iv. Acetylcysteine must be continued until (1) acetaminophen concentrations are undetectable (less than 10 mcg/mL), (2) LFTs are trending downward, and (3) markers of synthetic function are improving, preferably back to normal/baseline.
 - (a) Be sure to communicate units when discussing acetaminophen concentrations to avoid the potential for inappropriate treatment. Some laboratories report acetaminophen concentrations in milligrams per deciliter rather than micrograms per milliliter, which is a 10-fold difference (15 mg/dL = 150 mcg/mL).
 - (b) It is recommended to obtain repeat laboratory tests 2 hours before the end of the third bag (see Select Antidotes section).
 - (c) Continue with rate of last bag for an additional 16 hours if the above endpoints are not met.

Patient Case

3. P.W. is a 16-year-old female adolescent who presented to the ED at 8 a.m. with nausea, vomiting, and abdominal pain. She admitted ingesting an entire bottle of extra-strength acetaminophen the day before in an attempt to harm herself. Laboratory test results were as follows: sodium 142 mEq/L, potassium 4.2 mEq/L, chloride 110 mEq/L, carbon dioxide 20 mEq/L, blood urea nitrogen 10 mg/dL, serum creatinine 0.6 mg/dL, aspartate aminotransferase 1700 IU/L, and alanine aminotransferase 1650 IU/L. Her acetaminophen concentration was 40 mcg/mL (20 hours after ingestion). Which is the most appropriate course of action for P.W.?
- Withhold acetylcysteine therapy because her acetaminophen concentration is normal, and the history in patients who try to commit suicide is unreliable.
 - Initiate acetylcysteine therapy because her LFTs are elevated and her acetaminophen concentration is in the toxic range.
 - Send the patient to a psychiatric unit; no additional laboratory tests are necessary.
 - Withhold acetylcysteine therapy for now, but continue to monitor LFTs.

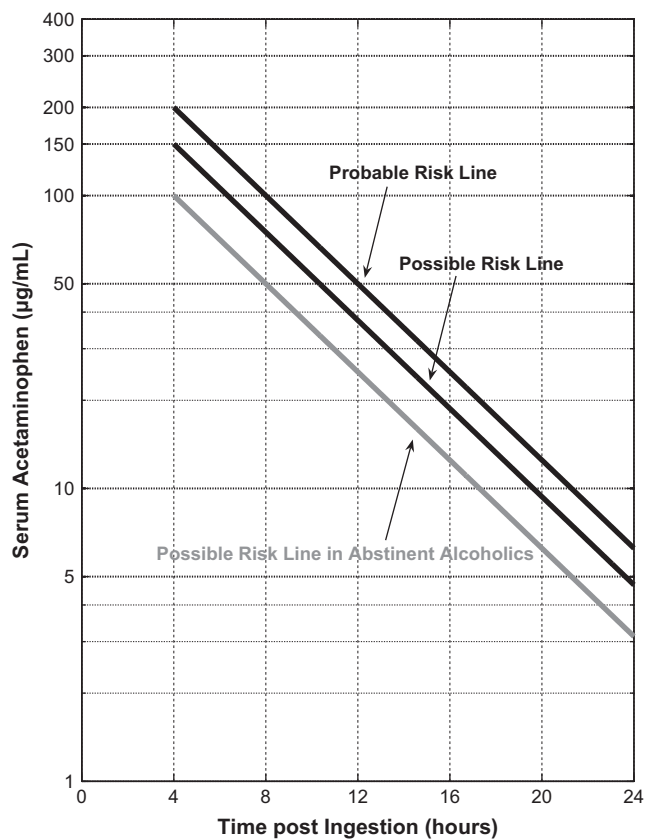


Figure 2. Rumack-Matthew nomogram. Acetaminophen serum concentration versus time after acetaminophen ingestion. The values above the Rumack-Matthew line (200mcg/mL at 4 hours) are associated with increased risk of hepatotoxicity. Initiation of acetylcysteine is recommended above the possible risk line (150mcg/mL at 4 hours). This version of the nomogram also depicts a proposed possible-risk line in patients with a history of alcoholism.

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3. Anticoagulants/thrombolytics
 - a. Epidemiology:
 - i. Anticoagulant exposures have increased by 35% over the past decade (Clin Toxicol (Phila) 2020;58:1360-541).
 - ii. Oral anticoagulants are most commonly used in adults.
 - iii. The increased availability of these medications potentially increases the risk of exploratory exposures in children..
 - b. Mechanism of toxicity: Anticoagulants inhibit specific factors along the intrinsic and extrinsic coagulation pathways, leading to increased risk of bleeding.
 - c. Signs and symptoms of toxicity
 - i. Nose bleeds, bleeding from gums or skin punctures, bruising, altered mental status (intracranial hemorrhage), abdominal distension and tenderness (retroperitoneal hemorrhage), respiratory distress (hemothorax)
 - ii. Clinically significant bleeding that warrants reversal, as defined by the American College of Cardiology, is any of the following:
 - (a) Associated with hemodynamic instability
 - (b) Requiring greater than 2 units of packed RBCs
 - (c) Sudden decreases in Hgb greater than 2 g/dL
 - (d) Occurrence in anatomically critical sites (i.e., intracranial, spinal, retroperitoneal, thoracic)
 - d. Management:
 - i. Supportive measures to control the bleeding (manual compression, local therapy, surgery) and discontinuation of anticoagulants. In overdose (accidental or intentional) within 2 to 4 hours, gastrointestinal decontamination with activated charcoal should be considered. With clinically significant bleeding, specific reversal agents are administered. Currently no guidelines exist for management of pediatric bleeding in this setting.
 - (a) Warfarin:
 - (1) Phytonadione (vitamin K₁) 30 mcg/kg intravenously
 - (2) Fresh frozen plasma or prothrombin complex concentrates (see below) to control emergent bleeding
 - (A) Oral factor-Xa inhibitors:
 - Factor Xa (recombinant), inactivated-zhzo
 - Dosing, safety, and efficacy not yet established in pediatrics
 - Fresh frozen plasma or prothrombin complex concentrates (see below) to control emergent bleeding
 - (B) Dabigatran:
 - Idarucizumab
 - Dosing, safety, and efficacy not yet established in pediatrics
 - Fresh frozen plasma or activated prothrombin complex concentrates (see below) to control emergent bleeding
 - (C) Heparins: Reversed with protamine sulfate
 - Unfractionated heparin (UFH):
 - Protamine dosed according to Table 4.
 - Maximum dose 50 mg and maximum rate of 5 mg/minute
 - Measurement of activated partial thromboplastin time 2–4 hours after protamine administration can be used to assess efficacy of reversal. A repeat dose of 0.5 mg of protamine per 100 units of heparin can be considered if activated partial thromboplastin time remains elevated.

- Enoxaparin:
 - Protamine dosed according to Table 4.
 - If prolonged activated partial thromboplastin time, 2–4 hours after initial protamine dose, repeat 0.5 mg for each 1 mg enoxaparin

Table 4. Protamine Sulfate Dosing for Heparin and Enoxaparin Reversal

UFH Bolus (time after dose)	Protamine Dose (mg per 100 units of UFH)
Immediately	1
30–60 min	0.5–0.75
60–120 min	0.375–0.5
> 120 min	0.25–0.375
<i>After UFH continuous infusion</i>	1 mg per 100 units of UFH in previous 2–3 hr
Enoxaparin (time after dose)	Protamine Dose (mg per 1 mg of enoxaparin)
< 8 hr	1
8–12 hr	0.5
> 12 hr	Reversal unnecessary unless prolonged activated PTT

UFH = unfractionated heparin.

(D) Thrombolytic agents (e.g., alteplase, tenecteplase)

- Cryoprecipitate (usual dose 1 unit/5 kg or 5–10 mL/kg)
 - Antifibrinolytics: There is limited evidence in pediatrics and dosing recommendations are not established
 - Aminocaproic acid (usual dose 50–100 mg/kg intravenously over 10–60 minutes)
 - Tranexamic acid (usual dose 10–15 mg/kg intravenously over 20 minutes)
 - ii. Both 4-factor (II, VII, IX, X) and 3-factor (II, IX, X) prothrombin complex concentrates, though routinely used in managing bleeding from warfarin and factor-Xa inhibitors in adults, lack established safety and efficacy in pediatrics.
 - iii. Activated prothrombin complex concentrates, namely factor VIII inhibitor bypassing activity, has established dosing (50 units/kg) for control of bleeding in pediatrics, though it lacks data in reversal of anticoagulation related bleeding.
 - e. Management pearls: The risk of thrombosis should be weighed with the benefit to administering any reversal agent. It is also important to consider resuming anticoagulation as soon as possible and if clinically appropriate.
4. Aspirin
- Epidemiology: Salicylate overdoses continue to be a problem in the United States. In 2020, U.S. poison control centers received over 15,000 calls for human exposures involving salicylates. Patients poisoned by salicylates tend to decompensate quickly, potentially progressing to metabolic acidosis, renal failure, and death. Salicylates include aspirin, bismuth subsalicylates, and methyl salicylates. Oil of wintergreen is a common source of methyl salicylate.
 - Mechanism of toxicity: Central stimulation of the respiratory center causes hyperventilation and resultant respiratory alkalosis, which may lead to dehydration and compensatory metabolic acidosis. In addition, the uncoupling of oxidative phosphorylation, glucose, and fatty acid metabolism may cause profound anion gap metabolic acidosis.

- c. Signs and symptoms of toxicity
 - i. Early: Tachypnea, hyperpnea, respiratory alkalosis, gastritis, dehydration, tinnitus, fever, elevated heart rate, agitation, and confusion
 - ii. Late: Metabolic acidosis, noncardiogenic pulmonary edema, renal insufficiency, hepatotoxicity, coma, and seizure. (Note: Metabolic acidosis may occur earlier in pediatric patients than in adults because pediatric patients have a lesser degree of respiratory alkalosis.)
- d. Management
 - i. Patients who ingest more than 150 mg/kg (or 6.5 g; whichever is less) at one time or 100 mg/kg/day over 2 days should be monitored in the ED for at least 6 hours.
 - ii. Obtain a baseline salicylate concentration, a BMP, and, for severe cases, a blood gas. Serum salicylate concentrations greater than 30 mg/dL require close monitoring and alkalization with sodium bicarbonate.
 - iii. Alkalization is achieved with sodium bicarbonate bolus or infusion to maintain serum pH above 7.4.
 - (a) Urinary excretion is improved with alkaline urine (urine pH 7.5–8).
 - (b) Bicarbonate also keeps salicylates ionized, thus decreasing their ability to distribute into tissue.
 - iv. Dialysis if patient has detectable concentrations and one of the following: severe metabolic acidosis, unresponsive hypotension, significant altered mental status with no other identifiable cause, evidence of end-organ injury (e.g., renal, cerebral, pulmonary), or concentration greater than 100 mg/dL
 - v. Monitor salicylate concentrations and BMPs every 1–2 hours until a peak and decline is observed.
- e. Management pearls
 - i. Be sure to communicate units when discussing salicylate concentrations to avoid the potential for inappropriate treatment (i.e., mg/dL vs. mcg/mL).
 - ii. Avoid medications that cause respiratory depression and subsequent hypoventilation (e.g., benzodiazepines, opioids). Reducing the patient's respiratory compensation mechanisms can increase salicylate's distribution to tissues. If mechanical ventilation is necessary, use extreme caution, and hyperventilation should be maintained.
 - iii. Monitor and replace potassium to help kidneys excrete hydrogen ions.
 - iv. Pharmacobezoars (mass of clumped-up pills) may form in the stomach. A rise or plateau in concentrations could indicate a pharmacobezoar.

Patient Case

4. A.J., a 15-year-old male adolescent (weight 70 kg), told his parents that he ingested a handful of tablets from a bottle of 100-count chewable 325 mg aspirin. It was a full bottle, and about one-half of the tablets remain. The parents brought the adolescent and the bottle to the ED within 30 minutes of the ingestion. On examination, he was tachypneic, with a respiratory rate of 36 breaths/minute, but otherwise had normal vital signs. He had some guarding on abdominal examination and had vomited several times before arrival. A BMP and venous blood gas (VBG) are reported back within normal range. His salicylate concentration was 10 mg/dL. Which would be the next best step in treating A.J.?
- A. His salicylate concentration was low and his VBG was normal, so he may be sent home.
 - B. Renal should be consulted because he should undergo dialysis immediately.
 - C. A salicylate concentration should be repeated in 2 hours.
 - D. Because he ingested a potentially toxic dose of aspirin, he should be given syrup of ipecac.

5. β -Blockers
 - a. Epidemiology: Cardiovascular drugs remain among the top 10 exposures for adults as well as among the top 10 fatalities in poison control center data.
 - b. Mechanism of toxicity: β -Receptor blockade resulting in reduced chronotropy/ionotropy and subsequent bradycardia and hypotension. Receptor selectivity is dose-dependent and is diminished in an overdose setting.
 - c. Signs and symptoms of toxicity
 - i. Bradycardia
 - ii. Hypotension
 - iii. QRS interval widening on ECG with agents that have sodium channel blockade activity (e.g., propranolol)
 - iv. Prolonged QT interval on ECG with agents that cause potassium channel blockade activity (e.g., sotalol)
 - v. Sinoatrial and atrioventricular node blockade
 - vi. Hyperkalemia
 - vii. Hypoglycemia (especially in children and patients with diabetes)
 - viii. Seizures with lipid-soluble agents (e.g., propranolol)
 - ix. Bronchospasm
 - x. Possible coma and death with severe overdoses
 - d. Management: Ingestions of more than a maximum single therapeutic dose must be monitored at a health care facility.
 - i. Supportive care (intravenous fluids and atropine sulfate for symptomatic bradycardia)
 - ii. Glucagon (off-label use), considered first line for β -blocker-induced bradycardia (see Select Antidotes section for dosing)
 - iii. Vasopressors (e.g., norepinephrine, epinephrine, dopamine)
 - iv. Calcium (intravenous) for hypotension

Patient Case

Questions 5 and 6 pertain to the following case.

K.W. is a 2-year-old girl who was found with her grandmother's pill reminder box. Her grandmother takes lisinopril, a multivitamin without iron, metoprolol, metformin, melatonin, and warfarin. Three days of pills had been left in the box, and no pills now remain.

5. Which of the grandmother's medications is most likely to be harmful to K.W?
 - A. Warfarin.
 - B. Metformin.
 - C. Metoprolol.
 - D. Lisinopril.
6. If K.W. developed hypotension and bradycardia, which would be the most logical treatment algorithm to consider?
 - A. Fluids/atropine, then glucagon, then calcium.
 - B. Fluids/atropine, then glucagon, then epinephrine.
 - C. Epinephrine, then glucagon, then fluids.
 - D. Fluids/atropine, then epinephrine, then lipid emulsion therapy.

- v. Consider high-dose insulin euglycemic therapy (off-label use) for refractory cases (see Select Antidotes section for dosing).
 - vi. May also consider lipid emulsion therapy (off-label use) for refractory cases
 - e. Management pearls: Because sotalol and extended-release β -blockers may have delayed toxicity, they should be monitored for at least 24 hours. Monitor serum glucose and potassium closely if using high-dose insulin, euglycemic therapy.
- 6. Calcium channel blockers
 - a. Epidemiology: Cardiovascular drugs remain among the top 10 exposures for adults as well as among the top 10 fatalities in poison control center data.
 - b. Mechanism of toxicity: Direct antagonism of L-type calcium channels of the heart and vascular smooth muscle, leading to decreased calcium influx and resultant reduction of cardiac contractility, loss in vascular tone, and slowed atrioventricular and sinoatrial node activity. Also, inhibits insulin release from pancreatic islet cells
 - c. Signs and symptoms of toxicity: Bradycardia (more with non-dihydropyridines), hypotension, distributive shock (more with dihydropyridines), second- or third-degree atrioventricular block, hyperglycemia, stupor, confusion, and possible coma and death with severe overdoses
 - d. Management: Ingestions of more than a maximum single therapeutic dose must be monitored at a health care facility.
 - i. Supportive care (fluids/atropine)
 - ii. Calcium (maintain ionized calcium around 1.5 times normal)
 - iii. Vasopressors (e.g., norepinephrine, epinephrine, dopamine)
 - iv. High-dose insulin euglycemic therapy (off-label use) (see Select Antidotes section for dosing)
 - v. Glucagon (off label use) for bradycardia (see Select Antidotes section for dosing)
 - vi. May consider lipid emulsion therapy (off-label use) for refractory cases
 - e. Management pearls: Avoid administration of calcium chloride peripherally due to risk of venous sclerosis. If peripheral administration is necessary, use calcium gluconate. In addition, careful monitoring of patient's volume status is important due to the high fluid volumes attributed to insulin and vasopressor infusions.
- 7. Caustics
 - a. Epidemiology: Caustic agents account for a broad class of substances (alkali and acids) that can be found throughout the home setting. Since passage of the PPPA in the 1970s, which requires child-resistant packaging for all caustics at a concentration of 2% and above, the incidence and severity of caustic exposures in children have dramatically decreased.
 - b. Mechanism of toxicity: Acids (pH less than 2) cause coagulation necrosis, resulting in eschar formation that protects from deeper penetrating burns. Alkalis (pH greater than 12) cause liquefactive necrosis allowing for further penetration and resulting in more extensive tissue damage.
 - c. Signs and symptoms of toxicity:
 - i. Immediate: Severe pain of the lips, mouth, tongue, throat, chest, and abdomen. Can also cause excessive drooling, vomiting, and erosive effects resulting in hematemesis and clinically significant bleeding. Swelling of the upper respiratory tract can result in stridor and respiratory compromise. In severe cases, there is potential for GI perforation.
 - ii. Delayed: Survivors of the immediate phase can develop esophageal strictures (scarring) weeks to months later. This leads to chronic pain, malnutrition, and esophageal carcinoma.
 - d. Management
 - i. Airway: If intubation is necessary, this procedure should be done with laryngoscope to avoid inadvertent perforation of pharynx or larynx.
 - ii. Decontamination: Removing affected clothing, irrigating skin and eyes. Prior to hospital arrival, encourage oral dilution with water and do not induce emesis. Dilution may help reduce injury from substance adhering to the esophagus.

- iii. Endoscopy within 12–24 hours may be necessary to determine the extent of damage; further treatment and follow-up (for stricture formation) are determined according to the grading of damage.
 - (a) Grade I esophageal injuries typically lack ulcer formation and do not develop strictures.
 - (b) Grade II burns have ulcerations of submucosal layer (grade IIa are noncircumferential, grade IIb are circumferential).
 - (c) Grade III injuries are defined as having deep ulcerations and necrosis and are at greatest risk of strictures, which may develop over weeks to months after injury.
- iv. The use of intravenous corticosteroids theoretically reduces the risk of esophageal strictures; however, data on their efficacy are limited. Studies show that steroids may worsen the outcomes of grade III esophageal burns through increased risk of infection and thinning of tissue; therefore, steroids should be avoided in that group. However, there is some evidence that steroids in combination with antibiotics may be beneficial in grade IIb burns.
- e. Management pearls
 - i. Neutralization methods in the management of caustic ingestions are contraindicated. An exothermic reaction may occur that could worsen the extent of the injury.
 - ii. Gastric decontamination measures should be avoided due to the risk of additional esophageal injury and aspiration or airway damage.
- 8. Foreign bodies
 - a. Epidemiology: Foreign bodies (e.g., toys) are among the top 10 ingestions in pediatric patients reported to poison control centers each year. Fortunately, most foreign body ingestions are unlikely to cause complications. However, we pay special attention to the following ingestions: button batteries, coins, lead-based objects, magnets, sharp objects, and expand-in-water toys.
 - b. Mechanism of toxicity
 - i. Button batteries: Ingestions are very serious. Can cause tissue damage as soon as 2 hours after ingestion.
 - ii. Coins: Not typically problematic, but there have been cases of asymptomatic esophageal or airway entrapment.
 - iii. Lead-based objects: Can lead to systemic toxicity.
 - iv. Magnets: When more than one is swallowed, the attraction of magnets in adjacent loops of bowel may cause bowel wall necrosis.
 - v. Sharp objects: May cause direct tissue damage
 - vi. Expand-in-water toys: Although unlikely, may lead to bowel obstruction
 - c. Signs and symptoms of toxicity: Depend on the foreign body. However, many of the symptoms are a result of airway or GI obstruction or damage.
 - d. Management
 - i. Button batteries: Emergent radiograph to confirm that the battery is not lodged in the esophagus and follow-up radiograph to make sure the battery has cleared within 4–10 days. Potential emergency endoscopic removal is necessary if battery has not passed the pylorus. A recently published study of live piglets showed that honey and sucralfate decreased the severity of burn injury caused by button battery ingestion. The national button battery management guidelines have been updated to include these therapies(<https://www.poison.org/battery/guideline>).
 - ii. Coins: Radiograph to confirm coin is not lodged in the esophagus, should pass without intervention. Potential endoscopic removal is necessary if coin has not passed the pylorus.
 - iii. Lead-based objects: Radiograph to confirm location, consider WBI to decrease GI transit time and decrease opportunity for absorption and systemic toxicity. Obtain a venous lead concentration. May also consider use of acid neutralizer (e.g., histamine-2 blocker, proton pump inhibitor), which may help decrease extent of absorption but will not likely be beneficial if using WBI

- iv. Magnets: Radiograph to determine whether several magnets were swallowed. If several magnets have been ingested and are past the stomach and patient is asymptotic, may consider WBI for prompt expulsion from GI tract. If several magnets are in esophagus or stomach, or if patient is symptomatic, may consider endoscopic removal
 - v. Sharp objects: Radiograph and potential endoscopic or surgical removal
 - vi. Expand-in-water toys: Although unlikely, may lead to bowel obstruction. Radiolucent imaging is not helpful. Monitor for signs of bowel obstruction, and if evident, surgical intervention may be necessary.
 - e. Management pearls: Delayed recognition and treatment of button battery ingestions have been deadly.
9. Iron
- a. Epidemiology: Fortunately, packaging regulations and education on the harm that iron can cause have greatly reduced the incidence of iron poisoning in children. However, because significant poisonings still occur, they must be managed promptly and appropriately.
 - b. Mechanism of toxicity: Iron is a GI irritant that can result in significant mucosal irritation and injury. Systemic toxicity manifests as lactic acidosis and organ failure. Iron's cellular toxicity is thought to be a result of oxidative and free radical injury.
 - c. Signs and symptoms of toxicity: Iron overdose has been described in five stages (not all patients have all five):
 - i. 0.5–2 hours: GI symptoms due to corrosive effects, including vomiting, diarrhea. Hematemesis, shock, and acidosis are also possible at this stage. Absence of symptoms in first 6 hours probably eliminates likelihood of severe iron toxicity
 - ii. Latent phase 6–24 hours: Potentially symptom free; however, ongoing cellular organ damage is occurring
 - iii. 2–12 hours: Shock, severe acidosis, fever, coma, death
 - iv. 2–3 days: Hepatic failure
 - v. 2–8 weeks: Delayed symptoms associated with initial caustic injury (e.g., strictures, intestinal obstructions)
 - d. Management: Patients who have ingested more than 40 mg/kg of elemental iron or who are having moderate to severe symptoms should be evaluated in the hospital.
 - i. Consider abdominal radiograph to determine the potential for GI decontamination in the setting of potentially toxic tablet ingestion. Liquid and chewable tablets are not typically radiopaque; therefore, lack of visual of iron on radiograph does not rule out iron ingestion. Charcoal not effective; consider WBI if situation appropriate
 - ii. Initiate deferoxamine therapy at 15 mg/kg/hour intravenously if the patient has severe symptoms or if the serum iron concentration is greater than 500 mcg/dL.
 - (a) Deferoxamine binds with ferric iron to produce a ferrioxamine complex that is excreted in the urine.
 - (b) This complex, which is excreted renally, may cause the urine to turn reddish brown.
 - e. Management pearls
 - i. For acute iron toxicity, use intravenous route for deferoxamine administration, especially in patients with poor hemoperfusion, because absorption and distribution of intramuscular and subcutaneous routes may be altered.
 - ii. The latent phase may provide a false sense of reassurance that the patient is safe from harm, but significant morbidity and mortality can result, especially with early discharge.
 - iii. Adverse effects of deferoxamine: Prolonged (greater than 24 hours) high doses (greater than 15 mg/kg/hour) may lead to acute respiratory distress syndrome. In addition, patients with chronic iron overload are at an increased risk of *Yersinia enterocolitica* sepsis because this organism requires iron stores for growth. This risk is thought to be worsened by deferoxamine

therapy because it fosters the growth of *Yersinia*. Monitor accordingly. Infusion rates greater than 40 mg/kg/hr are associated with hypotension.

10. Lead

- a. Epidemiology: Despite the dramatic reduction in the prevalence and severity of lead poisoning since the removal of lead from gasoline and paint in the 1970s, lead remains an important environmental health concern for young children, especially in lower socioeconomic families. Therefore, children should have routine lead screens at 1 and 2 years of age, especially those whose families participate in poverty assistance programs. The Centers for Disease Control and Prevention recommends public health action for concentrations greater than 5 mcg/dL. Antidotes used in lead poisoning are British anti-lewisite (BAL, or dimercaprol), edetate calcium disodium, and succimer. BAL is a metal chelator that crosses the blood-brain barrier. Edetate calcium disodium is also a metal chelator, but it is administered intravenously and does not cross the blood-brain barrier.
- b. Mechanism of toxicity: Lead toxicity affects many organ systems through a variety of complex mechanisms, through its affinity for electronic donor ligands, interference with calcium-mediated metabolic pathways, and mutagenic and myogenic effects in mammalian cells.
- c. Signs and symptoms of toxicity (in children)
 - i. Concentration 1–25 mcg/dL: Decreased IQ and impaired neurobehavioral development, but many are asymptomatic
 - ii. Concentration 25–60 mcg/dL: Impaired cognition, behavior, balance, headache, impaired growth and hearing, anemia
 - iii. Concentration 60–80 mcg/dL: Hyperirritable behavior, intermittent lethargy, vomiting, and abdominal pain
 - iv. Concentration greater than 80 mcg/dL: Persistent vomiting, nephropathy, neuropathy, and encephalopathy
- d. Management
 - i. WBI should be considered in acute ingestions.
 - ii. Asymptomatic
 - (a) Concentration 5–45 mcg/dL: Review home and school environment, educate, and follow concentrations closely.
 - (b) Concentration greater than 45 mcg/dL: Consider treating with oral succimer at 350 mg/m²/dose (or 10 mg/kg/dose) given three times daily for 5 days and then twice daily for 14 days. Round doses to the nearest 100 mg.
 - iii. Symptomatic without encephalopathy: May try oral succimer or intravenous edetate calcium disodium at a dose of 1000–1500 mg/m²/day divided into two to four doses or given as a continuous infusion if intolerant of succimer
 - iv. Encephalopathy (progressive headache, somnolence, seizures, coma): Treat with BAL at 75 mg/m² given intramuscularly every 4 hours and intravenous edetate calcium disodium given 4 hours after the initial dose of BAL; continue to overlap therapy at least 3–5 days. Studies suggest that the combination of BAL and edetate calcium disodium is more effective than edetate calcium disodium alone.
- e. Management pearls
 - i. Patients typically have difficulty with adhering to succimer because of its poor palatability.
 - ii. Succimer is available only as capsules; may be opened and mixed with soft foods or juice; use of chilled food or beverage may improve palatability
 - iii. Edetate calcium disodium has many aliases (e.g., calcium disodium versenate or calcium EDTA). Avoid using the abbreviation *EDTA* to avoid confusion with disodium EDTA (which could result in life-threatening hypocalcemia).
 - iv. BAL is administered intramuscularly and is very painful. Do not use in patients with a peanut allergy due to coformulation with peanut oil.

Patient Case

7. L.N. is a 4-year-old girl who presented to the ED with new-onset seizures, one of which was witnessed by ED triage staff. She recently moved with her family from India to the United States. Her mother reported that L.N. has had signs of impaired cognition and worsening, aggressive behavior for the past several months. An abdominal radiograph was unremarkable. A computed tomography scan revealed encephalopathy. A serum lead concentration was 90 mcg/dL. Which would be the most appropriate course of therapy for L.N.?
- A. Oral succimer alone.
 - B. WBI followed by edetate calcium disodium.
 - C. Edetate calcium disodium followed by BAL.
 - D. BAL followed by continuous edetate calcium disodium.

11. Rabies

- a. Epidemiology
 - i. Rabies cases have been on a steady decline since 1950 because of the widespread immunization of dogs and available prophylactic regimen.
 - ii. Potential sources of wildlife exposure include bats, raccoons, skunks, foxes, coyotes, and bobcats.
 - iii. The incubation period in humans averages 1–3 months.
- b. Mechanism of toxicity
 - i. The rabies virus can be spread only by saliva and brain or nervous tissue.
 - ii. The most common mode of transmission is a bite from a virus-containing host.
- c. Signs and symptoms of toxicity: Anxiety, radicular pain, dysesthesia or pruritus, hydrophobia, and dysautonomia
- d. Management
 - i. Postexposure prophylaxis: Rabies is 100% preventable with appropriate medical care. Ideally, prophylaxis should be initiated within 24 hours of exposure.
 - (a) Recommended for all patients bitten by a high-risk animal
 - (b) Recommended for all sleeping people and unattended children present in a room with a bat, given that bat bites may be painless and are difficult to detect
 - (c) Passive prophylaxis: Human rabies immune globulin (HRIG), 20 units/kg locally infiltrated around wound, if possible. If not possible or no visible wound, HRIG should be administered intramuscularly at a site distant from the vaccine administration site
 - (d) Active prophylaxis: Human rabies vaccine, 1 mL intramuscularly on days 0, 3, 7, and 14 after exposure
 - ii. Treatment
 - (a) Neither the human rabies vaccine nor the HRIG improves outcome once symptoms have manifested.
 - (b) Supportive care
 - (c) Survival from a rabies infection is very rare.

Patient Case

8. A.O. is a 3-month-old girl who was sleeping in her parents' bedroom. A.O.'s father awoke in the middle of the night to find a bat flying around in the bedroom. On examination, there is no evident bite mark or wound. Which statement best describes the most appropriate management strategy?
- A. No prophylaxis is necessary because there is no visible bite.
 - B. Initiate prophylaxis with HRIG and human rabies vaccine within 24 hours.
 - C. Initiate prophylaxis with HRIG and human rabies vaccine within 7 days.
 - D. Initiate just the human rabies vaccine; HRIG is not necessary because there is no visible bite.

12. Snakebites

- a. Epidemiology: Most venomous snakes in the United States are in the Viperidae family (subfamily Crotalinae), which includes the eastern and western diamondback rattlesnakes (*Crotalus adamanteus* and *C. atrox*), Mojave rattlesnakes (*Crotalus scutulatus*), copperheads (*Agkistrodon contortrix*), and cottonmouths or water moccasins (*Agkistrodon piscivorus*).
- b. Mechanism of toxicity: Venom contains enzymes, peptides, amino acids, metallic ions, lipids, and carbohydrates. Clinical manifestation from envenomation depends on the snake species and the amount of venom injected.
- c. Signs and symptoms of toxicity (varies depending on species of snake): Intense pain, swelling at site of bite, weakness, dizziness, nausea, vomiting, altered mental status, paresthesia, muscle fasciculations, tachycardia, visual disturbances, coagulopathy, pulmonary edema, and hypotension.
- d. Management
 - i. Frequently monitor local swelling, muscle strength, complete blood cell count (CBC), and PT, PTT, and INR.
 - ii. Administer tetanus vaccine as indicated.
 - iii. Call the poison control center (1-800-222-1222 in the United States) to determine whether administration of antivenin is necessary and to help coordinate procurement of such (especially for exotic, venomous snakebites).
 - (a) Bites from venomous snakes native to the United States (North American crotalids) can be treated with Crotalinae polyvalent immune Fab (ovine) (CroFab), or Crotalide Immune F(ab')₂ (Equine) (Anavip), according to their respective package inserts.
 - (b) Antivenin exerts its action by binding to the venom. Therefore, dosing is not based on the size of the patient; rather, a flat dose is repeated in 1-hour increments until clinical improvement is noted and progression of swelling has stopped; then maintenance dosing will begin. The two different U.S. Food and Drug Administration (FDA)-approved antivenin products are derived from different animal sources, with different dosing strategies:
 - (1) Anavip(R) [equine derived]:
 - (A) Initial: 10 vials
 - (B) Maintenance: 4 vials as needed; Note: Administer over 60 minutes. Covers *Bothrops asper* and *Crotalus durissus*
 - (2) CroFab(R) [ovine derived]:
 - (A) Initial: 4–6 vials
 - (B) Maintenance: 2 vials every 6 hours (for a total of three doses) Note: Administer over at least 1 hour. Covers *C. atrox*, *C. adamanteus*, *C. scutulatus*, and *A. piscivorus*. Maintenance dose not proven beneficial in copperhead bites

- e. Management pearls
 - i. Patients with significant blood dyscrasias requiring antivenin should be monitored (physical examination, CBC) for 2–4 days and possibly for up to 2 weeks after discharge for symptom recurrence.
 - ii. The FDA-approved snake antivenins available in the United States are not indicated for use in exotic snake bites. If the suspected snake is exotic or not within that subfamily (e.g., the coral snakes, which are in the Elapidae subfamily), contact the poison control center for assistance in locating appropriate antivenin, if available.
 - iii. Anaphylaxis and serum sickness are potential risks of antivenin therapy. Anavip is contraindicated in patients with hypersensitivity to horses, and CroFab is contraindicated in patients with hypersensitivity to sheep, pineapple, papaya, or alpha gal.
 - iv. Of the two available antivenins, one is not considered superior to the other because of the lack of head-to-head clinical trials. Pharmacokinetic considerations include differences in half-life (equine: 5.5 days vs. ovine: 12–23 hours). Although the ovine-derived product comes from snakes in the United States, the equine product is derived from snakes in Mexico. However, the equine product is FDA approved for the North American pit viper bites.
- 13. Spider Bites
 - a. Epidemiology: While most spiders possess venom glands, few have fangs long enough to penetrate human skin. In the United States, the most dangerous spiders include widow spiders (*Latrodectus* spp.), brown recluse (*Loxosceles*; central/southeastern United States), and tarantulas. Oftentimes, unexplained skin lesions are falsely attributed to spiders; however, the most common etiology is community-acquired methicillin-resistant *Staphylococcus aureus*. Admission is rare for any spider bite.
 - b. Mechanism of toxicity: In general, spider venoms are extremely potent but dose delivered is small.
 - i. Tarantula bites are often very painful due to size, but rarely cause envenomation. Urticating hairs can cause local allergic reactions.
 - ii. Widow venom: Contains alpha-latrotoxin, which causes opening on nonspecific cation channels, increasing influx of calcium, and release of acetylcholine to motor endplate.
 - iii. Brown recluse venom: Digestive enzymes and sphingomyelinase D (cytotoxic)
 - c. Signs and symptoms of toxicity: Most bites are minimally toxic and may cause self-limited local inflammation and mild systemic symptoms, including chills, malaise, and nausea
 - i. Widow: Mild erythema, target lesion (i.e., bull's eye ring), progressing pain, cramping, muscle fasciculations. May mimic myocardial infarction. Symptoms wax and wane and persist for 12–72 hours.
 - ii. Recluse: Bull's eye ring, necrotic arachnidism (slowly healing skin ulcers), hemolysis (sphingomyelinase D). Onset of necrosis takes up to 72 hours and may persist for weeks.
 - d. Management
 - i. Wound cleansing and cool compress
 - ii. Tetanus prophylaxis
 - iii. Widow:
 - (a) Pain management with opioid analgesics and muscle cramping with benzodiazepines. Questionable efficacy of skeletal muscle relaxants
 - (b) Antivenom (*Latrodectus mactans*):
 - (1) Indication: Envenomation-induced severe hypertension or muscle cramping refractory to above therapies; envenomation in pregnancy (due to risk of severe muscle spasms and risk of spontaneous abortion)
 - (2) Usual dose: 1 vial per dose (not dosed based on weight)
 - (3) A skin test for horse serum sensitivity should be performed by using a 1:10 dilution of antivenom.

- iv. Recluse: Hospital admission with systemic symptoms (e.g., chills, myalgia, generalized rash) to monitor for hemolysis and renal failure. Necrotic arachnidism is managed with standard wound care with use of appropriate antimicrobial for secondary infections. Early prophylactic excision is not indicated.
- e. Management pearls:
 - i. Despite the availability of an antivenom for widow envenomation, this therapy is rarely used due to high risk of anaphylaxis. Additionally, symptomatic treatments are usually adequate. Contraindications include hypersensitivity to horse serum and severe reactive airway disease.
 - ii. Dapsone has been proposed for management of necrotic arachnidism (reducing severity of ulcers), though this treatment is nonbeneficial and carries a high risk of methemoglobinemia.
- 14. Tricyclic antidepressants (TCAs)
 - a. Epidemiology: Although TCA use has decreased with the advent of newer antidepressants (e.g., selective serotonin reuptake inhibitors), the severity of clinical manifestations associated with inadvertent exposures and with intentional overdoses continues to be alarming.
 - b. Mechanism of toxicity: Central and peripheral antagonisms at muscarinic receptors cause anticholinergic syndrome (see Table 3), blocking of fast sodium channels leads to arrhythmias, and antagonist activity at the α_1 -adrenergic receptors leads to a decrease in vascular resistance.
 - c. Signs and symptoms of toxicity: Anticholinergic syndrome, hypotension, prolonged QRS, prolonged QT, arrhythmias, seizures, coma, and death
 - d. Management
 - i. Infants and children who ingest TCAs should be referred to a health care facility for evaluation if the amount ingested exceeds a dose of 5 mg/kg, except for desipramine (more than 2.5 mg/kg), nortriptyline (more than 2.5 mg/kg), protriptyline (more than 1 mg/kg), or trimipramine (more than 2.5 mg/kg).
 - ii. Supportive care
 - (a) Seizures: Benzodiazepines
 - (b) Hyperthermia: Cooling protocols (antipyretics unlikely to have much effect)
 - (c) Prolonged QRS greater than 100 milliseconds: Treat with sodium bicarbonate 1–2 mEq/kg intravenously, as needed, to maintain a serum pH of 7.45–7.55; consider lidocaine if refractory ventricular dysrhythmia occurs despite appropriate management with sodium bicarbonate.
 - (d) Hypotension: Fluids and sodium bicarbonate
 - e. Management pearls
 - i. Physostigmine to reverse the anticholinergic effects is contraindicated in TCA ingestions; it may aggravate cardiac complications and lower the seizure threshold.
 - ii. Do not use class Ia or Ic antiarrhythmics because they further block sodium channels and can aggravate cardiotoxicity. Similarly, avoidance of phenytoin to treat seizures is recommended due to sodium channel blockade and potential lowering of seizure threshold.

F. Select Antidotes

1. Acetylcysteine

- a. Indication: Use in acetaminophen overdose. Oral and intravenous are considered equivalent from an efficacy perspective.
- b. Mechanism of action: Acts as a glutathione precursor to help reduce the amount of NAPQI available, thereby reducing cellular damage. Studies have shown that it is most effective when initiated within 8–10 hours after ingestion; however, acetylcysteine therapy has sometimes appeared to be efficacious even with delayed initiation.
- c. Dosing (see package insert for a more detailed weight-based dosing chart)

Table 5. Dosing Regimens for Intravenous and Oral Acetylcysteine

Route	Intravenous	Oral
First dose	150 mg/kg over 1 hr	140 mg/kg
Repeat doses	50 mg/kg (12.5 mg/kg/hr) over 4 hr 100 mg/kg (6.25 mg/kg/hr) over 16 hr	70 mg/kg every 4 hr ×17 doses
Total duration	21 hr	72 hr

- i. Intravenous dosing
 - (a) Dilute according to the package insert or acetadote.net.
 - (b) Off-label concentration: To accommodate standardized concentration for dispensing and to simplify preparation and administration, you may consider establishing an institution-wide standard concentration and dosing of a 3% solution at a rate of 150 mg/kg/hour x 1 hour, 12.5 mg/kg/hour x 4 hours, followed by 6.25 mg/kg/hour x 16 hours.
 - ii. Oral dosing: Dilute to 5% solution before administration. Cola is best to mask sulfur odor. Ice cold, with lid, through straw may also help
 - iii. Reminder: Do not stop infusion or oral dosing until it has been documented that the patient has an undetectable acetaminophen concentration, LFTs are trending downward, and INR is less than 1.5.
 - d. Adverse reactions
 - i. Oral: Nausea, vomiting, diarrhea
 - ii. Intravenous: Flushing, rash, nausea, vomiting, rarely anaphylactoid reactions
2. Flumazenil
- a. Indication: Reversal of benzodiazepine overdose. However, because benzodiazepine overdoses do not typically result in depressed respiratory status, reversal is often not necessary. Flumazenil is commonly used as a reversal agent in general anesthesia or conscious sedation but less often in the overdose setting.
 - b. Mechanism of action: Competitive inhibition at the benzodiazepine subtype of the γ -aminobutyric acid receptor
 - c. Dosing: 0.01 mg/kg/dose (maximum 0.2 mg) intravenously given over 30 seconds; may repeat every minute until optimal response (maximum dose 3 mg in 60 minutes)
 - d. Adverse reactions: Flushing, palpitations, agitation; may potentiate seizures or withdrawal in susceptible patients (includes those taking chronic benzodiazepine therapy and TCA overdoses)
3. Fomepizole
- a. Indication: Ethylene glycol or methanol poisoning. It may be initiated in the following circumstances:
 - i. Methanol or ethylene glycol concentration more than 20 mg/dL
 - ii. Reliable history with blood concentrations pending
 - iii. Metabolic acidosis with unexplained osmolar gap (early) or anion gap (delayed-2–4 hours after ingestion)
 - b. Mechanism of action: Inhibition of alcohol dehydrogenase, preventing the metabolism of methanol and ethylene glycol to their toxic metabolites, formic acid for methanol and oxalic and glycolic acid for ethylene glycol
 - c. Dosing: 15 mg/kg (up to 1.5 g) intravenously x 1, followed by 10 mg/kg every 12 hours; increase dose to 15 mg/kg every 12 hours if therapy needs to continue beyond four doses (can undergo auto-induction of metabolism after four or more doses). Drug is dialyzable; modify frequency of dosing (manufacturer recommends increase to every 4 hours during dialysis).
 - d. Adverse reactions: Headache, nausea, vomiting, phlebitis, transient elevations in transaminases or triglycerides with repeat dosing

4. Glucagon
 - a. Indication: β -Blocker or calcium channel blocker overdose
 - b. Mechanism of action: Improves chronotropy and inotropy by increasing cardiac cyclic adenosine monophosphate, independent of the β -adrenergic receptor or calcium channel's antagonized state
 - c. Dosing: Administer bolus over 3–5 minutes; titrate infusion to achieve adequate hemodynamic response.
 - i. Children: 0.03–0.15 mg/kg; then infusion of 0.07 mg/kg/hour (maximum 5 mg/hour)
 - ii. Adolescents: 5–10 mg; then 1–5 mg/hour
 - iii. Adults: 3–10 mg; then 3–5 mg/hour
 - d. Adverse reactions: Nausea, vomiting, hypertension, tachycardia, hyperglycemia, hypersensitivity reaction, anaphylaxis
5. High-dose regular insulin (hyperinsulinemia-euglycemia therapy)
 - a. Indication: To improve hemodynamics in β -blocker and calcium channel antagonist overdoses that are unresponsive to conventional therapy for hypotension. Used in conjunction with dextrose (off-label use).
 - b. Mechanism of action: Improves inotropy and increases peripheral vascular resistance. Specific pharmacologic rationale is not well established.
 - c. Dosing: Use your institution's standard insulin infusion concentration. If fluid overload is of concern, may use concentrated insulin product (500 units/mL) (intravenous administration off-label). Must be diluted before use. Concentration of 16 units/mL in normal saline is stable for 14 days.
 - i. Bolus: 1 unit/kg, followed by an infusion at 0.1–1 unit/kg/hour
 - ii. All patients should also be initiated on a dextrose infusion at 0.5 g/kg/hour (if patients have blood glucose less than 200 mg/dL before starting, they should be loaded first and then initiated on infusion).
 - d. Adverse reactions: Hypoglycemia (may persist for several hours after cessation of insulin infusion), hypokalemia, fluid overload, hyponatremia
6. Lipid emulsion therapy
 - a. Indication: Potential improvement in hemodynamic measures in overdose situations, after all other measures have failed (off-label use), particularly in local anesthetic, TCA, and bupropion overdoses. Possibility for use with beta-blockers and calcium channel blockers, though expert consultation is recommended.
 - b. Mechanism of action: Not fully understood. Primary thought is the "lipid sink theory," which is that the lipids bind to lipid-soluble agents, inhibiting their ability to bind to receptors, thus decreasing the severity of toxic effects.
 - c. Dosing: 1.5-mL/kg bolus (maximum 100 mL) over 2–3 minutes; if clinical response, may start infusion at 0.25–0.5 mL/kg/minute for up to 60 minutes (maximum 1 L over 60 minutes)
 - d. Adverse reactions: Pancreatitis, increased LFTs, cyanosis, lipid overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly, and shock), potential laboratory interference (try to obtain critical laboratory test results before administration)
7. Naloxone
 - a. Indication: Reversal of respiratory suppressant effects of opioids and possible reversal of the effects of clonidine overdose
 - b. Mechanism of action: Competes and displaces opioids from mu-opioid receptors
 - c. Dosing (intramuscular, subcutaneous, intravenous, intranasal; off-label: intraosseous, endotracheal)
 - i. Full reversal: 0.1 mg/kg/dose (maximum 2 mg), repeat every 2–3 minutes as needed. Full reversal dose appropriate for most pediatric exploratory ingestions unless medical history indicates a potential tolerance to medications, in which case partial reversal as outlined in the text that follows may be more appropriate

- ii. Partial reversal: 0.001–0.01 mg/kg/dose (maximum 0.04–0.4 mg); repeat every 2–3 minutes as needed. (Consider partial reversal for patients who may be having adverse effects [e.g., respiratory suppression], but still with ongoing pain source and/or tolerance from long-term use)
 - iii. Continuous infusion may be considered in the setting of long-acting opioid ingestion (e.g., methadone, extended-release oxycodone, fentanyl patch ingestion). Dose by the amount in milligrams of effective intermittent dose administered hourly (e.g., if it took 2 mg to reverse patient, consider a rate of 2 mg/hour). It has also been proposed to consider an infusion rate of two-thirds the bolus dose administered hourly, with a half-bolus dose repeated as necessary.
 - d. Adverse reactions: Significant withdrawal symptoms may occur in patients tolerant of opioid agonists.
8. Octreotide
- a. Indication: Treatment of sulfonylurea-induced hypoglycemia refractory to glucose therapy. Treatment with intravenous dextrose should continue throughout therapy (off-label use).
 - b. Mechanism of action: Reduces insulin release from pancreatic β -cells
 - c. Dosing
 - i. Adult: 50–100 mcg subcutaneously or intravenously every 6–12 hours as needed
 - ii. Children: 1–1.25 mcg/kg subcutaneously or intravenously every 6 hours as needed for low blood glucose
 - iii. Most patients require one to three doses for adequate management. Some may require a continuous infusion at up to 100–125 mcg/hour.
 - d. Adverse reactions: Injection-site pain is the most common when used for this indication because the well-known adverse effect profile is associated more with chronic administration. For other indications (longer term), its use can result in gallbladder disease, GI effects, and cardiovascular complications.
9. See Table 6 for a comprehensive listing of antidotes and levels of efficacy.

Table 6. Summary List of Antidotes and Efficacy

Toxins		Antidotes	Efficacy ^a
Cardiac	Beta blockers	Glucagon hydrochloride	C
	Calcium channel blockers	Calcium chloride/gluconate	C
	Cardiac glycosides (e.g., digoxin)	Digoxin immune Fab	B
Neurologic	Anticholinergics (e.g., diphenhydramine)	Physostigmine	A
	Benzodiazepines	Flumazenil	A
	Isoniazid	Pyridoxine	C
	Lead	Succimer	A
		Calcium disodium edetate	B
		Dimercaprol (BAL)	B
	Organophosphates/carbamates/nerve agents	Atropine sulfate Pralidoxime Chloride (organophosphates only)	B A
	Opiates/opioids	Naloxone hydrochloride	A
	Valproic Acid	Levocarnitine (IV)	B

Table 6. Summary List of Antidotes and Efficacy (*continued*)

	Toxins	Antidotes	Efficacy ^a
Anticoagulants	Acquired coagulation factor deficiency	4-factor PCC ^b Activated PCC/3-factor PCC ^b	A B
	Dabigatran	Idarucizumab ^b	B
	Heparins (i.e., UFH, LMWH)	Protamine sulfate	C (UFH) A (LMWH)
	Oral factor-Xa Inhibitors (i.e., apixaban/ rivaroxaban)	Coagulation factor Xa (recombinant), inactivated-zhzo ^b	—
	Thrombolytics (e.g., alteplase, tenecteplase)	Aminocaproic/tranexemic acid	—
	Warfarin	Phytonadione	A
Antiplatelets	Aspirin/P2Y ₁₂ Inhibitors	Desmopressin	C
Other	Envenomation	Centuroides (scorpions) Crotalidae polyvalent immune Fab (snakes)	A B
	Cyanide	Hydroxycobalamin Sodium nitrite/sodium thiosulfate	B C
	Hydrofluoric acid	Calcium chloride/gluconate	C
	Iron	Deferoxamine mesylate	A
	Methotrexate	Leucovorin Glucarpidase	B B
	Nondepolarizing neuromuscular blockers (i.e., rocuronium, vecuronium)	Sugammadex	--
	Sulfonylureas	Octreotide	A
	Toxic alcohols (e.g., ethylene glycol, methanol)	Ethanol Fomepizole	B B
Syndromes	Drug-induced methemoglobinemia	Methylene blue	B
	Serotonin syndrome	Cyproheptadine	C

BAL = British anti-lewisite; IV = intravenous; LMWH = low molecular weight heparin; PCC = prothrombin complex concentrate; UFH = unfractionated heparin; — = unestablished efficacy.

^aStrength of evidence: A, good-quality randomized controlled trials and systematic reviews; B, prospective, nonrandomized trials, cohorts, or case-control studies; C, case series/reports.

^bCurrently safety and efficacy is not established in pediatrics.

G. Substance Use Disorders

1. Epidemiology: Adolescents have an increased susceptibility to partaking in risky behaviors due to the early development of the brain's emotional response and reward systems. Substance use in this group is associated with risk of delinquency, teenage pregnancy, sexually transmitted disease, violence, trauma, and mental health problems. Table 7 highlights the prevalence of use of certain substances in the high school population.
2. Substance use disorders are recognized by the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (see Box 2) for alcohol, hallucinogens (e.g., LSD), inhalants, marijuana, nicotine, opioids, phencyclidine (i.e., PCP), stimulants (e.g., amphetamines)
3. Management
 - a. Nonpharmacological therapies
 - i. Behavioral therapies
 - (a) Adolescent community reinforcement approach

- (b) Cognitive-behavioral therapy
- (c) Contingency management
- (d) Motivational enhancement therapy
- (e) Twelve-step facilitation therapy
- ii. Family-based approaches
 - (a) Basic strategic family therapy
 - (b) Family behavior therapy
 - (c) Functional family therapy
 - (d) Multidimensional family therapy
 - (e) Multisystem therapy
- b. Pharmacological therapies: Medications found to be effective in treating addiction are not approved by the FDA in adolescents. However, some therapies are often used off-label in this population. In particular, guidelines recommend consideration of treating adolescents with opioid use disorder with the full range of treatments, including medications. Table 8 highlights potential therapies for select substance use disorders.

Table 7. Prevalence of Substance Use Behaviors Among High School Students in 2019. No Changes Have Been Detected in the Last Decade Unless Otherwise Noted

Substance	Current Use % (Previous 30 d)	Lifetime Use %
Alcohol	29.2 ^a	—
Marijuana	21.7	36.8
Prescription opioids (misuse)	7.2	14.3
Cocaine	—	3.9 ^a
Heroin	—	1.8 ^a
Methamphetamine	—	2.1 ^a
Synthetic marijuana	—	7.3 ^b

^aDecreased in last decade.

^bDecreased in last 5 yr.

Box 2. Criteria for Diagnosis of Substance Use Disorder (Two or More)

Hazardous use	Social/interpersonal problems	Neglecting major role of use
Legal problems	Tolerance	Using larger quantities
Repeated attempts to quit	Time spent using	Physical/psychological complications
Activities given up	Craving	Withdrawal ^a

^aNot included for inhalants and hallucinogens.

Table 8. Potential Treatments for Specific Substance Use Disorders

Alcohol Use Disorder	
Acamprosate	• Potential activity by modulating glutamate • Reduces likelihood of relapse • 666 mg PO 3 times daily • Recommended to start as soon as abstinence is attained, continue during any relapse • Bypasses hepatic metabolism, may be used in hepatic dysfunction
Disulfiram	• Aldehyde dehydrogenase inhibitor • Only for individuals seeking abstinence; contraindicated with alcohol and in history of seizures • 250 mg PO daily • Consumption of alcohol within 12–24 hr of dose results in increased acetaldehyde, leading to tachycardia, flushing, headache, vomiting • Generally not first-line • Consider products and medications that may contain alcohol (e.g., mouthwashes, alcohol hand sanitizers, elixirs)
Naltrexone	• Opioid antagonist that is associated with reduced likelihood of relapse and possibly reduces craving for alcohol • 50 mg daily PO or 380 mg monthly depot intramuscular injection; no head-to-head comparisons of formulation • Well tolerated with mild GI side effects, but there are reports of hepatotoxicity. Use is not recommended in patients with acute hepatitis or liver failure • Consideration of concomitant opioid use disorder
Nicotine Use Disorder	
Bupropion sustained release	• Dopamine and norepinephrine reuptake and nicotinic acetylcholinergic receptor inhibitor to reduce withdrawal symptoms • 150 mg daily for 3 d, increase to BID, for up to 12 wk • Contraindicated in seizure disorders, history of eating disorders • Appropriate to use together with nicotine replacement therapy
Nicotine replacement therapy	• Delivery of nicotine as gum, lozenge, inhaler, nasal spray, patch • Intent to partially replace nicotine obtained through cigarettes
Varenicline	• Partial nicotine receptor agonist and antagonist • Approved in ages 17 yr and older • 1 mg PO BID • Not recommended for use in combination with nicotine products; caution should be taken in patient with psychiatric illness
Opioid Use Disorder	
Buprenorphine	• Partial opioid agonist with ceiling effect on euphoria and toxicity • Approved in ages 16 yr and older • Induction dose 2–4 mg PO, increased in 2–4 mg increments for resolution of withdrawal symptoms (if started without withdrawal symptoms, may precipitate withdrawal); maximum 24 mg/d • Abuse potential when crushed and injected (unless formulated with naloxone) • Providers require federal X-waiver registration in order to prescribe for OUD (now exempt if treating up to 30 patients at a time)

Table 8. Potential Treatments for Specific Substance Use Disorders (*continued*)

Opioid Use Disorder	
Methadone	• Long-acting mu opioid agonist • Dose ranges from 10 to 30 mg daily (federal maximum of initial dose is 30 mg); titrated to control of withdrawal • Prone to abuse and significant opioid overdose risk • Barriers to adherence include daily clinic assessment
Naltrexone	• Long acting opioid antagonist aiming to prevent relapse • Dosing for PO and IM is the same in alcohol use disorder • No role in management of acute withdrawal

BID = twice per day; GI = gastrointestinal; IM = intramuscularly; OUD = opioid use disorder; PO = by mouth.

Patient Case

Questions 9 and 10 pertain to the following case.

R.V. is a 17-year-old male adolescent (weight 100 kg) found down in his bathroom. His grandfather's verapamil pill bottle, filled the day before, was found empty next to him. He was brought to the ED, where his systolic blood pressure was in the 70s mm Hg and heart rate was 30 beats/minute. Electrocardiogram revealed sinus bradycardia. He was given fluids, atropine, and calcium gluconate boluses; his blood pressure improved to 90/50 mm Hg, and his heart rate improved to 50 beats/minute. Serum ionized calcium concentration after the bolus was 2.5 mg/dL.

9. Which is the most appropriate next step in treating R.V.?
 - A. Do nothing; his vital signs have stabilized.
 - B. Give another calcium bolus.
 - C. Administer lipid emulsion therapy.
 - D. Initiate high-dose insulin euglycemic protocol.

10. High-dose insulin euglycemic therapy is initiated at some time in R.V.'s course at a rate of 1 unit/kg/hour, with a dextrose 25% infusion of 0.5 g/kg/hour. His hypotension has resolved and remained stable for the past 8 hours without vasopressor therapy; however, he has required two dextrose 50% boluses to treat a blood glucose concentration less than 50 mg/dL. His blood glucose drops below 50 mg/dL for a third time. Which is the best strategy to manage R.V.'s high-dose insulin euglycemic therapy?
 - A. Discontinue the high-dose insulin infusion and dextrose therapy.
 - B. Continue the high-dose insulin euglycemic therapy, but increase the infusion rate of the dextrose 25% bag.
 - C. Discontinue the high-dose insulin infusion, but continue the dextrose infusion.
 - D. Continue the high-dose insulin euglycemic therapy, but consider decreasing the insulin rate.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

This patient's symptoms are consistent with an anticholinergic toxidrome; thus, diphenhydramine is likely involved (Answer B is correct). The patient is tachycardiac and hyperthermic and has dry mucous membranes and decreased bowel sounds. The anticholinergic symptoms with the report of recent exposure to an over-the-counter medication suggest diphenhydramine. Acetaminophen and ibuprofen are not likely to produce these symptoms (Answers A and C are incorrect). Rhinovirus is not likely to cause hypertension and tachycardia solely (Answer D is incorrect).

2. Answer: D

No gastric decontamination measures are warranted because the patient already has symptoms, which indicates that absorption has already occurred, and his mother reports giving several doses of the medication during the past 48 hours (Answer D is correct; Answers A–C are incorrect).

3. Answer: B

Given that the ingestion of a toxic dose of acetaminophen was relayed in the patient's history and that LFTs indicate hepatic injury, acetylcysteine therapy should be initiated immediately (Answer B is correct). Although histories can be unreliable, the clinical evidence of hepatic injury shows that acetylcysteine is warranted (Answers A and C are incorrect). Acetylcysteine should be initiated as soon as possible because its efficacy will decrease further out from the time of ingestion (Answer D is incorrect). However, there have been reports that initiating acetylcysteine therapy more than 24 hours after ingestion were of benefit.

4. Answer: C

The patient ingested a potentially toxic dose of aspirin and is mildly symptomatic on presentation (Answer A is incorrect). Repeat salicylate concentrations should be obtained and repeated every 2 hours until a peak and decline is noted (Answer C is correct). The concentration and the patient's clinical presentation do not currently warrant dialysis (Answer B is incorrect). The patient is tachypneic on admission, so he might be at a higher risk of aspiration. Gastric decontamination should be avoided for this reason. Syrup of ipecac is not recommended in any circumstance (Answer D is incorrect).

5. Answer: C

Metoprolol is on the list of agents that can cause serious harm in one or two doses (Answer C is correct). Although warfarin is of concern, an antidote is available, and significant clinical effects are not expected (Answer A is incorrect). Metformin may cause lactic acidosis in an overdose setting, but bradycardia and hypotension can be caused by β -blockers, which have more immediate implications (Answer B is incorrect). Lisinopril ingestions in young children have rarely caused life-threatening effects (Answer D is incorrect).

6. Answer: B

As with any patient (except in severe cardiac failure), fluid boluses and atropine should be the first step in managing bradycardia (Answer B is correct; Answer C is incorrect). However, because β -blockade is occurring, glucagon is a best next step over epinephrine for more efficient and effective improvement in heart rate and hypotension (Answer D is incorrect). Although calcium may be used for a β -blocker overdose, it is not likely to precede a vasopressor such as epinephrine (Answer A is incorrect).

7. Answer: D

Given that the patient had an elevated lead concentration and was encephalopathic, the best option would be BAL (which will cross the blood-brain barrier) followed by edetate calcium disodium (Answer D is correct; Answer C is incorrect). Oral succimer is probably not currently a good option because the patient's symptoms are severe (Answer A is incorrect). Whole bowel irrigation is unnecessary because the lead poisoning in this case is probably from chronic exposure (Answer B is incorrect).

8. Answer: B

Both HRIG and human rabies vaccine are recommended for all sleeping people and unattended children present in a room with a bat because bat bites may be painless and difficult to detect (Answer B is correct). The Centers for Disease Control and Prevention also recommends prompt response and treatment within 24 hours (Answers A, C, and D are incorrect).

9. Answer: B

The patient's heart rate and blood pressure are not normal (Answer A is incorrect). Because the patient's serum calcium was slightly low, he should receive another bolus of calcium (Answer B is correct). From there, a vasopressor infusion (e.g., epinephrine) should be considered. Although high-dose insulin euglycemic therapy is effective in managing calcium channel blocker overdoses, it is unlikely to supersede calcium in a patient with low serum calcium (Answer D is incorrect). Likewise, lipid emulsion therapy should be considered a last resort (Answer C is incorrect).

10. Answer: C

This patient has been stable from a cardiovascular perspective for several hours off vasopressor therapy; therefore, his high-dose insulin is no longer needed, especially given the frequent episodes of hypoglycemia (Answer C is correct; Answers B and D are incorrect). The hypoglycemic effects will likely persist for a few hours after stopping the insulin infusion; thus, the dextrose infusion should not be discontinued right away (Answer A is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

Answer C is correct. If the patient and scenario indicate that it is appropriate to perform gastric decontamination, WBI is the most likely gastric decontamination measure to be used in iron overdoses. Charcoal does not bind to iron, and because of the invasiveness of gastric lavage, it would likely fall to behind WBI in many clinicians' preferences (Answers A and B are incorrect). The patient is asymptomatic and has potentially been exposed to a significant amount of iron to cause harm; therefore, it would be appropriate to try to have the patient drink as much of the WBI preparation as can be tolerated (Answer D is incorrect).

2. Answer: B

The patient has an elevated heart rate, mydriasis, dry mucous membranes, and decreased urinary output. The last two symptoms (dry membranes and decreased urinary output) help differentiate anticholinergics from sympathomimetics; hence, an anticholinergic medication is most likely involved in this patient's symptoms (Answer B is correct; Answer C is incorrect). Cholinergic ingestion would manifest with clinical signs and symptoms opposite of those described in this case (miosis, increased urinary output, and increased oral secretions) (Answer D is incorrect). Opioid exposures would present obtunded and with miosis (Answer A is incorrect).

3. Answer: D

Answer D is correct. Children younger than 6 years, mainly those who are 1–3 years of age, account for the most exposures reported to poison control centers. Because of children's oral exploration of their surroundings and desire to emulate adults, these exposures are often unintentional general (e.g., exploratory ingestions). Unintentional therapeutic exposures and malicious exposures also occur, but not to the same extent as unintentional general exposures (Answers A and B are incorrect). Children younger than 6 very rarely present with concerns for suicidal ideation (Answer C is incorrect).

4. Answer: A

Answer A is correct. Glyburide is on the list of medications that could harm a child in a single dose. Profound hypoglycemia can occur, especially in children who

have decreased glycogen stores and are at high risk of severe, persistent hypoglycemia. There is no role for home management of pediatric ingestions of glyburide. Although the other medications may be harmful at large-enough doses, one single dose is typically not cause for concern (Answers B–D are incorrect).

5. Answer: C

The first steps in treating any patient are the ABCs (airway, breathing, and circulation). The patient has signs of potential airway compromise from his unresponsive state, so he should be intubated (Answer C is correct). His cardiovascular system also needs to be addressed, but he has a pulse and a blood pressure (Answers A, B, and D are incorrect). He will need to receive a fluid bolus, followed by specific treatments for β -blocker overdoses (glucagon, followed by catecholamines, followed by calcium or high-dose insulin).

6. Answer: D

A concentration greater than 500 mg/dL is considered toxic and warrants treatment (Answer C is incorrect). Deferoxamine can be administered intravenously, subcutaneously, or intramuscularly. Intravenous administration is thought to be preferred to subcutaneous or intramuscular administration in severely poisoned patients because it is more reliable, eliminating the need for absorption before distribution (Answer B is incorrect). Deferoxamine is administered as a continuous infusion for severe iron toxicity (Answer A is incorrect); therefore, 15 mg/kg/hour intravenous continuous (Answer D) is most appropriate.

7. Answer: B

According to the Rumack-Matthew nomogram, concentrations greater than 150 mcg/mL at 4 hours after ingestion warrant acetylcysteine therapy (Answer B is correct). Obtaining a concentration before 4 hours will not capture the peak with certainty and therefore will not be useful with assessing risk with the Rumack-Matthew nomogram (Answer A is incorrect). The concentrations of 90 mcg/mL at 4 hours and 9 mcg/mL at 12 hours fall below the treatment line on the nomogram (Answers C and D are incorrect). The most difficult part of using the Rumack-Matthew nomogram is being able to trust the time since ingestion; hence, it is best to check LFTs also to monitor for hepatic damage. Also of importance,

the nomogram does not apply to chronic ingestions or to patients with underlying hepatic impairment.

8. Answer: B

The Centers for Disease Control and Prevention recommends both active and passive immunity for raccoon bites if the raccoon cannot be captured to rule out rabies. For patients with open wounds, HRIG should be administered directly into the wound (Answer B is correct; Answers A, C, and D are incorrect).

9. Answer: B

With the poison helpline, poison control centers in the United States assist both community members and healthcare providers by providing poison information and patient-specific recommendations (Answers A and D are incorrect). By doing this, poison centers are able to reduce unnecessary ED visits and healthcare associated costs (Answer C is incorrect). Due to the telehealth nature of poison centers, they do not perform confirmatory lab testing or provide direct patient care (Answer B is correct).

10. Answer: C

With the exception of bupropion, all the listed therapies play some role in managing a patient with opioid-use disorder (Answer A is incorrect). Naloxone is a reversal agent for opioids and is only to be used as a rescue therapy (Answer B is incorrect). Clonidine may play a role in symptomatic control but is not approved for managing opioid-use disorder (Answer D is incorrect). Buprenorphine is a medication for opioid-use disorder that is approved in ages 16 years and older (Answer C is correct).

GASTROENTEROLOGY

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Learning Objectives

1. Apply national guideline and consensus management strategies for the following pediatric gastrointestinal (GI) disorders, where applicable: gastroesophageal reflux disease (GERD), diarrhea, constipation, irritable bowel syndrome (IBS), Crohn disease (CD), ulcerative colitis (UC), short bowel syndrome (SBS), appendicitis, nausea and vomiting, and ulcers.
2. Design treatment and monitoring regimens for managing GERD in pediatric patients.
3. Identify causes of diarrhea in pediatric patients, and recommend appropriate treatment and supportive care management to prevent associated complications.
4. Generate appropriate prevention and treatment strategies for pediatric constipation.
5. Distinguish between and recognize the clinical criteria for the types of IBS in order to provide appropriate recommendations for each type.
6. Compare and contrast the different clinical signs and symptoms of UC and pediatric CD, and recommend corresponding treatment regimens.
7. Describe the influence of bowel length and residual function in the management of SBS, including pharmacotherapy and monitoring plans for diarrheal management in pediatric patients with SBS.

Abbreviations in This Chapter

BM	Bowel movement
CD	Crohn disease
EBV	Epstein-Barr virus
EEN	Exclusive enteral nutrition
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
H ₂ RA	Histamine-2 receptor antagonist
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBS-C	Constipation-predominant irritable bowel syndrome
IBS-D	Diarrhea-predominant irritable bowel syndrome
IBS-M	Mixed-type irritable bowel syndrome
NASPGHAN	North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition
NSAID	Nonsteroidal anti-inflammatory drug
OTC	Over-the-counter

PCD	Perianal Crohn disease
PN	Parenteral nutrition
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease
SBS	Short bowel syndrome
TNF	Tumor necrosis factor
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis

Self-Assessment Questions

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

1. A 15-year-old African American female adolescent (weight 51 kg) presents with a 2-month history of epigastric pain. She states that she likes to eat spicy foods and that she drinks caffeinated beverages three times a day but that she does not feel she has changed her eating habits since the symptoms began. The pain is unrelieved by eating, and she has tried over-the-counter (OTC) calcium carbonate with little relief. Which recommendation is best for this patient?
 - A. Have her eliminate spicy foods and carbonated beverages from diet.
 - B. Initiate famotidine 20 mg twice daily.
 - C. Initiate omeprazole 20 mg twice daily.
 - D. Refer her to a gastroenterologist.
2. An 8-month-old girl (weight 6.6 kg) with a 2-day history of diarrhea presents with decreased oral intake, "dry crying," and irritability. On physical examination, the mucosa is moderately dry, eyes are slightly sunken, skin turgor is decreased, and fontanelle is slightly reduced. Capillary refill is about 4 seconds. Her pre-illness weight is 7 kg (15.5 lb). Her mother states that she has not changed formulas (cow's milk based, lactose-containing formula) but wonders whether her daughter could be allergic to milk. She has not introduced any new foods to her child's diet. There has been a recent family history of gastroenteritis. Which is the best initial treatment for this patient?
 - A. Recommend to change to a soy-based formula.
 - B. Provide oral rehydration therapy.
 - C. Start intravenous fluid rehydration.
 - D. Initiate loperamide 1 mg with each loose stool.

3. A 4-year-old boy with cerebral palsy and severe developmental delay presents to the clinic for a follow-up appointment from 3 months ago. On questioning, his parents state that he has only stoolled an average of twice a week since his last clinic visit. They report that when he does have a bowel movement (BM), the stools are very hard, and he seems to have pain with defecation. Which is the best initial treatment for this patient?
 - A. 1 infant glycerin suppository as needed for constipation.
 - B. Docusate sodium 10 mg four times daily.
 - C. Mineral oil 120 mL twice daily.
 - D. Polyethylene glycol 1.5 g/kg daily for 3-6 days.
4. A 9-year-old girl presents with a 6-month history of abdominal pain at least once a week that occurs with a change in her bowel habits. She reports having hard, lumpy BMs whenever she has this abdominal pain. When asked about dietary habits, she says that she often eats at fast food restaurants "because it is fast." She is very involved in her school academic team and makes all A's on her report card. Which is the best initial treatment strategy for this patient?
 - A. Avoid high-fat food, discuss relaxation techniques, and begin psyllium.
 - B. Continue current diet, discuss relaxation techniques, and increase dietary fiber gradually.
 - C. Increase dietary fiber, begin polyethylene glycol, and initiate docusate sodium.
 - D. Initiate docusate sodium, bisacodyl suppositories, and citalopram.
5. An 11-year-old boy with newly diagnosed Crohn disease (CD) is admitted to the hospital for induction of remission secondary to weight loss and concern for disease progression. His Pediatric Crohn's Disease Activity Index score is 45. Which is the best induction regimen for this patient?
 - A. Methotrexate 15 mg/m² orally once weekly.
 - B. Mesalamine 50 mg/kg/day orally divided every 8 hours.
 - C. Prednisone 1 mg/kg/dose orally once daily.
 - D. Mercaptopurine 1 mg/kg/dose orally once daily.
6. A 13-year-old presents with a history of moderate ulcerative colitis (UC) and has been treated with corticosteroids for 1 week with a good response. The patient is able to swallow pills and has a documented reaction to sulfamethoxazole-trimethoprim. Which agent would be best for maintenance therapy?
 - A. Prednisone.
 - B. Mesalamine.
 - C. Sulfasalazine.
 - D. Azathioprine.
7. An 8-week-old, former 26 weeks' gestation, infant (weight 1760 g) developed surgical necrotizing enterocolitis on day of life 7. He had 100 cm of small intestine removed and his ileocecal valve removed. The patient has achieved only moderate growth while receiving parenteral nutrition (PN) and has had an increased number and volume of stools since starting low-volume continuous enteral feeds. The patient has received diphenoxylate and atropine at a dose of 0.3 mg/kg/day in four divided doses for 1 week without improvement. Which recommendation is best for this patient?
 - A. Increase diphenoxylate/atropine to 0.5 mg/kg/day in four divided doses.
 - B. Discontinue diphenoxylate/atropine.
 - C. Initiate octreotide 10 mcg/kg/dose intravenously every 12 hours.
 - D. Initiate ursodiol 10 mg/kg/dose orally every 8 hours.
8. A patient with a history of short bowel syndrome (SBS) with only a few centimeters of the terminal ileum remaining recently underwent an anastomosis and ostomy takedown. Of note, the rest of the bowel was unaffected and the colon is intact. The patient has been maintaining growth with increased enteral feeds and has weaned to 30% of total daily nutrition requirements given parenterally. However, the patient has had diarrhea and has skin breakdown in the diaper area refractory to wound care. Which recommendation is best for this patient at this time?

- A. Decrease enteral feeds and increase PN until diarrhea resolves.
 - B. Obtain B₁₂ concentrations and initiate B₁₂ replacement, if necessary.
 - C. Initiate cholestyramine 240 mg/kg/day in three divided doses.
 - D. Initiate loperamide 0.08 mg/kg/day in two or three divided doses.
9. A 7-year-old girl presents to the emergency department for right lower-quadrant abdominal pain, nausea, vomiting, fever, and inability to walk. Imaging and surgery confirm perforated appendicitis. Which postoperative antibiotic regimen is most appropriate for this patient?
- A. Metronidazole alone.
 - B. Ceftriaxone plus clindamycin.
 - C. Ceftriaxone plus metronidazole.
 - D. Meropenem alone.
10. A previously healthy 4-year-old girl presents with a history of intermittent vomiting occurring at least once a month for the past year. Each time this occurs, she vomits about 10 times for 24–48 hours. Some episodes have also occurred with an upper respiratory tract infection or otitis media, but each episode begins with nausea in the morning, followed by vomiting, abdominal pain, anorexia, and dizziness. Her mother has a history of migraine headaches. The child's medical history is otherwise negative, and on physical examination, her growth, neurologic examination, and vital signs are all normal. A basic metabolic panel is within normal limits, and her upper GI series was normal. In addition to lifestyle modification such as sleep hygiene, which is the most appropriate next step for this child?
- A. Amitriptyline.
 - B. Cyproheptadine.
 - C. Diphenhydramine.
 - D. Ketorolac.
11. A 7-year-old boy presents with peptic ulcer disease (PUD) and a positive rapid urease test. He has a history of iron-deficiency anemia and a family history of gastric cancer. The patient has no known drug allergies. Which is best for this child?
- A. Treatment not recommended until positive biopsy results.
 - B. Amoxicillin plus clarithromycin plus a proton pump inhibitor (PPI).
 - C. Amoxicillin plus metronidazole plus sucralfate.
 - D. Metronidazole plus bismuth subsalicylate plus a PPI.
12. A 3-month-old boy presents to the clinic with a 1-month history of spitting up after at least two feedings per day. The patient is otherwise healthy and has been able to finish all of his bottles (breast milk), despite spitting up. At this visit, he is at the 75th percentile for weight and height. Which is the best recommendation for this patient?
- A. Parental education, reassurance, anticipatory guidance.
 - B. 2-week trial of extensively hydrolyzed formula.
 - C. 2-week trial of famotidine therapy.
 - D. 4-week trial of lansoprazole therapy.
13. An 8-year-old boy with functional constipation has been treated successfully for impaction. The patient, a former 26 weeks' gestation NICU (neonatal intensive care unit) graduate, has a history of developmental delay secondary to small, bilateral intraventricular hemorrhages and chronic lung disease managed with inhaled corticosteroids and occasional diuretic therapy. He currently receives a regular diet supplemented with PediaSure. His bowel regimen before this recent impaction included docusate sodium syrup 75 mg twice daily and polyethylene glycol 17 g daily. The caregiver, who reports no adherence issues, asks for recommendations to avoid impaction in the future. Which is best for this patient?
- A. Bisacodyl 5 mg by mouth daily.
 - B. Lactulose 7.5 mL by mouth daily.
 - C. Magnesium citrate 100 mL by mouth daily.
 - D. Senna 10 mL by mouth daily.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5, 1.9

I. GASTROESOPHAGEAL REFLUX DISEASE**A. Epidemiology**

1. Regurgitation occurs daily in about 50% of infants younger than 3 months and resolves, in healthy infants, by 12–14 months of age.
2. Reflux symptom prevalence of 4.3% at 6 months of age, decreases to 2% by 18 months of age
3. 25% of all routine 6-month infant provider office visits involve discussion of reflux symptoms.

B. Definitions

1. Emphasis is placed on differentiating gastroesophageal reflux (GER) from gastroesophageal reflux disease (GERD) in the 2009 North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) guidelines. In the 2018 joint NASPGHAN and European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines, the definitions of regurgitation, reflux, and GERD were updated as reflected in the following text. The 2018 guidelines point out that it is often difficult to distinguish between GER and GERD in children, and even health care professionals use the terms interchangeably.
2. Regurgitation is the passage of refluxed gastric contents into the pharynx or mouth, which are sometimes expelled out of the mouth.
 - a. Effortless, non-projectile, can be forceful
 - b. Similar terms: “Spitting up,” “possetting,” and “spilling”
3. GER is the passage of gastric contents into the esophagus with or without regurgitation and vomiting (Table 1).
 - a. Normal physiologic process lasting less than 3 minutes
 - b. Occurs postprandially, no lasting symptoms
4. GERD: When GER leads to troublesome symptoms that affect daily functioning and/or complications (e.g., weight loss, pain)
5. Refractory GERD: GERD not responding to optimal treatment after 8 weeks

C. Pathophysiology and Pathogenesis

1. Occurs when the lower esophageal sphincter (LES) relaxes and swallowing does not occur appropriately, allowing stomach contents to pass into the esophagus
2. Neonates and infants have an increased risk of GER as a result of a shorter esophageal length, decreased LES tone, delayed gastric emptying, and immature peristalsis (Arch Dis Child Fetal Neonatal Ed 1996;75:F117-21).

Table 1. Clinical Associations and Signs and Symptoms of Reflux

Preterm neonates to infants < 1 yr	Apnea (preterm neonates) Failure to thrive Recurrent aspiration Wheezing Irritability/crying Arching (especially around feeding) Regurgitation Vomiting Food refusal Brief resolved unexplained event (BRUE)
Children 1–5 yr	Cough Abdominal pain Food refusal Regurgitation Recurrent pneumonia Tooth erosion
Children 6 yr to < 18 yr	Heartburn Epigastric pain Dysphagia Reflux esophagitis

Information from: Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49:498-547.

D. Diagnosis

1. History and physical examination

- a. Infants and toddlers have no diagnostic set of symptoms.
 - i. The Infant Gastroesophageal Reflux Questionnaire Revised diagnostic tool has also been used for symptom monitoring. It consists of 14 questions related to the signs and symptoms listed in Table 1 of *Clin Gastroenterol Hepatol* 2006;5:588-96.
 - ii. Rome IV criteria – Diagnostic for infant regurgitation and other GI disorders. For regurgitation, healthy infants between 3 weeks and 12 months of life need to present with both of the following:
 - (a) Regurgitation twice or more daily for 3 weeks or more
 - (b) No retching, hematemesis, aspiration, apnea, failure to thrive, feeding or swallowing difficulties, or abnormal posturing
 - iii. Differentiate between regurgitation and vomiting caused by GER and other factors. For example, bilious vomiting can be associated with obstruction; pyloric stenosis can have nonbilious emesis but is associated with a hypochloremic metabolic alkalosis.
 - iv. Attention to extraesophageal warning signs: Apnea, apparent life-threatening event, arching, failure to thrive – These would warrant additional workup.
 - v. Reflux does not cause unexplained crying or distressed behavior (irritability); other causes to rule out:
 - (a) Milk protein allergy
 - (b) Neurologic disorders
 - (c) Constipation
 - (d) Infection (commonly urinary tract infection [UTI])

- b. Diagnosis in children and adolescents may be based on a set of clinical symptoms similar to those in adults, including heartburn.
 - c. Rumination syndrome
 - i. Can occur in each age group
 - ii. Prevalence: 2%–7% in infants and toddlers
 - iii. Involves both habitual and voluntary regurgitation of stomach contents into the oral cavity
 - iv. Associated with self-stimulatory behavior; may occur in children and adults with neurologic impairment
 - v. Treatment often targets elimination of the need for the behavior.
 - vi. Should be suspected after 2 months of symptoms, and evaluation for malnutrition is needed
 - 2. Esophageal pH monitoring
 - a. Esophagitis diagnostic tool
 - b. Measures esophageal acid exposure
 - c. Does NOT correlate with severity
 - d. Useful in evaluating efficacy of antisecretory therapy and in infants/children with wheezing or other respiratory symptoms that may have symptoms aggravated by GER
 - e. If applicable, and in patients who are able, pH modification agents should be held during baseline pH probe assessments.
 - i. Proton-pump inhibitors should be held one week prior.
 - ii. H2RAs should be held 48 hours prior.
 - iii. Antacids can be taken the day before the procedure.
 - 3. Combined MII (multiple intraluminal impedance) and pH monitoring
 - a. Detects acid, weakly acid, and nonacid reflux episodes
 - b. Superior to pH monitoring alone (can be used when diagnosing esophagitis)
 - 4. Motility studies: Not useful for diagnosis of GER, but can be used to confirm other diagnoses that may mimic GER
 - 5. Endoscopy and biopsy
 - a. Best method for confirming reflux esophagitis is by visualizing breaks in the distal esophageal mucosa.
 - b. Absence of visual findings (mucosal erythema, pallor, and changed vascular patterns) or histologic findings (eosinophilia, elongated rete pegs, basilar hyperplasia) does not rule out GERD.
 - c. This testing is used to rule out other causes of esophagitis and to diagnose BE (Barrett esophagus) and/or complications.
 - 6. Barium contrast radiography: Not useful for GERD, but can be used to diagnose anatomic abnormalities of upper GI tract
 - 7. Nuclear scintigraphy, esophageal and gastric ultrasonography: Not recommended for diagnosis of GERD
 - 8. Empiric trial of acid suppression
 - a. Older children or adolescents with symptoms of GERD
 - b. Trial of PPI for up to 4 weeks
 - c. Note: Improvement does not confirm GERD diagnosis, and this is not approved in infants and younger children where symptoms are less specific.
- E. Treatment/Management
- 1. Lifestyle changes – Infant
 - a. Parental education, guidance, support
 - i. Prone positioning in the non-sleeping infant decreases esophageal acid exposure when measured by pH probe versus supine position; however, risk of SIDS (sudden infant death syndrome) outweighs benefit, and infants should be supine from birth to 12 months of age.

- ii. Evaluate volume of feeds. Avoidance of overfeeding and a trial of more frequent, lower-volume feeds are recommended.
 - iii. Breastfeeding mothers are encouraged to continue this practice when no alarm signs are present.
 - b. For poor weight gain and recurrent vomiting: Initial evaluation should also include diet history, urinalysis, complete blood cell count (CBC), serum electrolytes, blood urea nitrogen (BUN), and serum creatinine (SCr).
 - c. Milk protein sensitivity can be the cause of unexplained crying and vomiting in infants. If symptoms are not improved after the previously mentioned strategies and alarm signs are still absent, the 2018 guidelines suggest the following:
 - i. Formula-fed infants may benefit from a 2- to 4-week trial of extensively hydrolyzed protein formula to rule out cow's milk protein allergy. Eliminating maternal consumption of cow's milk for breastfed infants may also be recommended.
 - ii. Thickened formulas may decrease visible regurgitation, but they do not decrease the number of reflux episodes. The safety of thickeners must also be considered.
 - (a) Cereal based: Rice cereal is most common and is less likely to clog nipples. It is generally affordable and has been used for a long time. However, concerns exist with arsenic exposure (see information resources at www.fda.gov), and cereal-based thickeners are not good for breast milk because the amylases in breast milk will break down the thickener.
 - (b) Commercial thickeners: These thickeners may be used with breast milk, but warnings on the use of xanthan gum- and carob bean-based thickeners and the risk of necrotizing enterocolitis exist for premature and term infants.
 - d. Close follow-up with weight change and nutrition status is necessary.
 - e. If there is no weight gain, referral to a gastroenterologist is recommended. In addition, GER beyond 12 months of age generally warrants further testing for an alternative diagnosis.
 - f. The 2018 guidelines do not currently recommend other nonpharmacologic therapies, including massage therapy, prebiotics, probiotics, or herbal medications.
- 2. Lifestyle changes – Older children and adolescents
 - a. No evidence to support elimination of a food
 - b. Correct underlying contributors associated with symptoms of GERD:
 - i. Obesity – Inform caregivers excessive body weight is associated with an increased prevalence of GERD.
 - ii. Smoking avoidance
 - iii. Eat smaller meals (vs. large meal volume)
 - iv. No late-night eating
 - c. Prone or left-side sleeping position and/or elevation of the head of the bed (results similar to adult studies)
- 3. Pharmacologic therapies
 - a. Infants
 - i. No evidence to support empirically using acid suppression to treat irritable infants. The 2018 guidelines recommend that if there are no warning signs and no impact on feeding, growth, or meeting developmental milestones, no testing or acid suppression is needed.
 - ii. 2018 NASPGHAN guidelines recommend the following strategies:
 - (a) In the absence of alarm signs, continue parental counseling on expected duration of symptoms and nonpharmacologic management strategies.
 - (b) Evaluate for alarm signs, including esophagitis.
 - (c) After a 2- to 4-week trial of formula change or elimination of maternal consumption of cow's milk (in breastfed infants), referral to a pediatric gastroenterologist OR a 4- to 8-week trial of antisecretory therapy if the referral is not possible is recommended (symptom resolution with trial may also be placebo response).
 - (d) If symptoms improve with therapy, a medication wean is recommended.

- b. Children and adolescents
 - i. Occasional heartburn – On-demand therapy with buffering agents, sodium alginate, histamine-2 receptor antagonist (H_2 RA) (for occasional symptoms). H_2 RA most commonly used, cost-effective, tolerated with few adverse effects
 - ii. Recurrent heartburn – 4- to 8-week trial of PPI
 - (a) If symptoms resolve with trial, a slow wean is recommended. No specific tapering instructions are outlined in the guidelines.
 - (b) If heartburn persists after 3 months on PPI or recurs after therapy is discontinued, referral to gastroenterologist is recommended
 - iii. Esophagitis – Mild to severe, continue therapy for 12 weeks
 - c. Potential risks of acid suppression, particularly with PPI use, include increased risk of community-acquired pneumonia, small bowel overgrowth, GI infections (acute gastroenteritis, necrotizing enterocolitis, and *Clostridioides difficile*–associated diarrhea), vitamin deficiencies, and candidemia in premature neonates.
 - d. See Table 2 for a summary of pharmacotherapeutic agents.
 - e. Other therapies: Cisapride – Mixed serotonergic agent that increases gastric emptying and strengthens esophageal and intestinal peristalsis by facilitating the release of acetylcholine at synapses in the myenteric plexus
 - i. Clinical trials showed a reduction in the reflux index but a less consistent reduction in symptoms (Cochrane Database Syst Rev 2003;4:CD002300; J Gastroenterol Hepatol 2003;18:196-202; J Pediatr Surg 1987;22:931-4).
 - ii. Restricted to limited-access programs (and clinical trials), based on propensity to prolong corrected QT (QTc) interval on electrocardiogram (ECG) and increased risk of sudden death
4. Surgical therapy
- a. Gastrostomy tube with/without Nissen fundoplication – May benefit children with chronic-relapsing GERD and/or children with respiratory complications (asthma, recurrent aspiration related to GERD)
 - b. Indications:
 - i. Failure of optimized medical therapy
 - ii. Dependence on long-term medical therapy
 - iii. Significant nonadherence to medical therapy
 - iv. Pulmonary aspiration
 - v. Children at highest risk of GERD are also at highest risk of complications because of surgery (postoperative morbidity and failure).

Table 2. Select Pharmacotherapeutic Agents for GERD

Agents	Therapy Notes
Antacids – Buffer gastric acid	
Magnesium hydroxide and aluminum hydroxide	• Reduce heartburn and heal esophagitis; on-demand use • Avoid in renal failure because of accumulation and resulting toxicity; aluminum toxicity can also occur with prolonged use • Magnesium-containing products may also cause diarrhea
Calcium carbonate	• Chronic or high-dose ingestion of calcium carbonate can cause milk-alkali syndrome (hypercalcemia, alkalosis, renal failure) • Calcium-containing products may worsen constipation
Mucosal Surface Barriers – Mucosal healing by forming a protective gel coating by binding to exposed mucosa of peptic erosions	
Sucralfate	• Not recommended as sole treatment; usually add-on therapy with H₂RA or PPI for erosive esophagitis, little clinical evidence; adult study showed reduced symptoms in nonerosive esophagitis; pediatric data show sucralfate as effective as cimetidine for esophagitis • Aluminum salt may accumulate in renal failure • Can cause zinc and other nutrient deficiencies (including phosphorus and fluoride) with prolonged use. • Give other medications 2 hr before or 4 hr after sucralfate; administer on an empty stomach
H₂RAs – Decrease acid production by competitive inhibition of the histamine-2 receptors in gastric parietal cells	
Class notes: • Studies have shown association with H₂RAs and necrotizing enterocolitis in preterm infants • Tapering upon discontinuation is not needed • Reports of tachyphylaxis • Renal adjustment required • On-demand relief of symptoms; mild esophagitis; class effect for efficacy in treating mild esophagitis; gastric pH increases within 30 min of administration and lasts 6 hr (dosing should be BID or TID)	
Famotidine	• Compatible with PN
Cimetidine	• Rarely used secondary to adverse effects (gynecomastia, risk of liver disease, neutropenia, thrombocytopenia) and drug interactions because of inhibition of CYP enzymes

Table 2. Select Pharmacotherapeutic Agents for GERD (*continued*)

Agents	Therapy Notes
PPIs – Inactivate H ⁺ /K ⁺ -ATPase pump in parietal cells, inhibiting acid secretion (both basal and with meals)	
<i>Class notes:</i> • First-line maintenance therapy for GERD and chronic heartburn in children and adolescents; initial management of mild to severe erosive esophagitis (for 3 mo) • Efficacy superior to H₂RAs because of longer duration of action (inhibits acid secretion for up to 15 hr). Takes approximately 4 days for full onset of action. (Note: Some providers suggest overlapping with an H₂RA for 3 to 5 days.) Infants and younger children require higher per kilogram dosing • Discontinuation can be associated with acid rebound, so should be tapered gradually. Not associated with tolerance, but guidelines suggest tapering off over 4 wk when therapy is complete • Potential safety concerns with increased susceptibility to enteric infections (e.g., <i>C. difficile</i>) • Smallest effective dose should be used • Administer 15–30 min before first meal of the day (proton pumps are stimulated by a meal) • Metabolized by CYP 2C19 and 3A4 (2C19 activity is low at birth and reaches adult values at 6–12 mo of age; exceeds adult values at 1–4 yr of age; then returns to adult values at puberty) • PPIs decrease absorption of drugs requiring an acidic environment (itraconazole, griseofulvin) • Adverse effects: Headache, nausea, constipation, diarrhea; prolonged therapy (> 2 yr) has been associated with acute interstitial nephritis, parietal cell hyperplasia, vitamin B₁₂ deficiency, bone loss, hypomagnesemia • IV formulations not compatible with PN (pantoprazole, esomeprazole)	
Omeprazole	• Causes decreased clearance of carbamazepine (monitor concentrations if coadministering) and diazepam • FDA approved for use in severe erosive esophagitis in patients ≥ 1 mo • Omeprazole compounding kit contains sugar and may increase stooling in some patient populations
Esomeprazole	• Only PPI to have FDA approval for use in neonates and infants < 1 yr with GERD (off-label use of others common)
Lansoprazole	• Lansoprazole and omeprazole compounding kits contain sugar and may increase stooling in some patient populations • Extemporaneously compounded products may also be used and may be favored for insurance coverage and/or available without sugar for patients on ketogenic diet
Pantoprazole	• Available as IV formulation
Rabeprazole	• Rarely used
Dexlansoprazole	• Rarely used

Table 2. Select Pharmacotherapeutic Agents for GERD (*continued*)

Agents	Therapy Notes
Prokinetic Agents – Mechanisms vary by agent, but they facilitate gastric emptying	
Class notes: • Used for symptomatic improvement • Inferior efficacy to PPIs and H₂RAs alone • In combination with H₂RA or PPI, may be useful in patients with delayed gastric emptying	
Metoclopramide (dopamine receptor antagonist)	• Has a black box warning associated with its potential for extrapyramidal reactions and tardive dyskinesia and is not currently recommended by the NASPGHAN/ESPGHAN guidelines; adverse effects outweigh potential benefits for routine use; insufficient evidence of clinical efficacy • If metoclopramide must be used, adjunctive diphenhydramine may assist in managing the patient's extrapyramidal symptoms
Erythromycin (acts on motilin receptors)	• Works best on motility after initiation of enteral nutrition Associated with pyloric stenosis and drug-drug interactions, GI upset, hepatotoxicity, antibiotic resistance, arrhythmias (QTc prolongation – should monitor for drug-drug interactions with other QTc-prolonging medications and consider baseline ECG and follow-up for monitoring) • Prolonged use may lead to down-regulation of motilin receptors and tachyphylaxis. Studies using erythromycin for gastroparesis suggest short, or pulse, courses (e.g., 10 days on therapy, 20 days off therapy) to avoid this
Bethanechol (direct cholinergic agonist)	• Has unclear efficacy and adverse effects, including headache, malaise, abdominal cramps, belching, nausea, vomiting

BID = twice daily; GERD = gastroesophageal disease; HS = at bedtime; H₂RA = histamine-2 receptor antagonist; IV = intravenous(ly); PN = parenteral nutrition; PO = oral(ly); PPI = proton pump inhibitor; q = every; QD = once daily; QID = four times daily; TID = three times daily.

Information from: Takemoto CK, Hodding JH, Kraus DM. Pediatric & Neonatal Dosage Handbook, 18th ed. Hudson, OH: Lexicomp, 2011; Vandenplas Y, Rudolph CD, Di Lorenzo C, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr 2009;49:498-547; Guillet R, Stoll BJ, Cotten CM, et al. Association of H₂-blocker therapy and higher incidence of necrotizing enterocolitis in very low birth weight infants. Pediatrics 2006;117:e136-42; Simon B, Ravelli GP, Goffin H. Sucralfate gel versus placebo in patients with non-erosive gastro-oesophageal reflux disease. Aliment Pharmacol Ther 1996;10:441-6; Cucchiara S, Minella R, Franco MT, et al. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Arch Dis Child 1993;69:655-9; Arguelles-Martin F, Gonzalez-Fernandez F, Gentles MG. Sucralfate versus cimetidine in the treatment of reflux esophagitis in children. Am J Med 1989;86:73-6.

Patient Cases

1. A 4-month-old boy presents with a history of spitting up three times per day for the past 3 weeks. His mother reports no apnea or posturing, and the patient has met all developmental milestones and maintained good growth velocity during the past few months. In fact, his mother states that he is taking bottles every 3 hours and is sometimes hungry between feedings, for which the mother may give another half bottle. However, the patient does have some irritability with these episodes. Which is best for this patient?
 - A. Educate the parents on overfeeding and warning signs.
 - B. Change to an anti-regurgitation formula.
 - C. Initiate famotidine therapy.
 - D. Initiate metoclopramide therapy.
2. A 10-year-old boy (weight 50 kg) presents to the clinic with a recent history of heartburn and epigastric pain. He reports an increase in frequency during the past month and states that symptoms are present most days. Which is best for this patient?
 - A. Initiate lifestyle change addressing obesity.
 - B. Initiate lifestyle change addressing obesity, and initiate omeprazole 20 mg/day for 4–8 weeks.
 - C. Initiate lansoprazole 30 mg/day for 4–8 weeks.
 - D. Initiate famotidine 20 mg.

II. DIARRHEA

- A. Epidemiology
 1. Diarrhea is a leading cause of morbidity and mortality among children.
 2. Worldwide, diarrheal diseases account for 1 in 9 pediatric deaths.
 3. Developing countries have the greatest percentage of mortality because of the struggle to provide clean drinking water, hygiene, and overall health and nutrition, leading to an environment favorable for pathogens.
 4. Infectious and noninfectious causes
- B. Etiology
 1. Characterized by 3 or more loose, watery stools per day (or more than normal for an individual)
 2. Many causes of acute and chronic diarrhea (Table 3)

Table 3. Common Causes of Diarrhea

Causes	Examples
Infectious	Viral Cytomegalovirus, adenovirus, rotavirus, norovirus Bacterial <i>Salmonella, Yersinia, Escherichia coli, Shigella, Campylobacter, C. difficile</i> Parasitic <i>Giardia, Entameba histolytica, Cryptosporidium, Microsporidia</i>
Toxins	<i>C. difficile</i> toxin Enterotoxins (from enteric organisms)
Exposures	Radiation enteritis Chemotherapy Laxative abuse Medications (antibiotics, magnesium-containing antacids) Tumor-associated increased secretion
Malabsorption	Pancreatic insufficiency Celiac disease Chronic liver disease Allergic enteropathy Glucose galactose transport defect SBS Lactose intolerance
IBD	UC CD Eosinophilic gastroenteritis Allergic colitis
Genetic-metabolic disorders	Malabsorption syndromes
Chronic nonspecific diarrhea/ toddler diarrhea	Exacerbated by a low-fat diet, high-carbohydrate diet in infants to toddler age
Overfeeding	Large quantity of carbohydrate-rich food in infancy combined with decreased amylase concentration

CD = Crohn disease; IBD = inflammatory bowel disease; SBS = short bowel syndrome; UC = ulcerative colitis.

Adapted with permission from: Piro CC. Diarrhea and constipation. In: Benavides S, Nahata M, eds. Pediatric Pharmacotherapy. Lenexa, KS: American College of Clinical Pharmacy, 2013:261-78.

3. Acute diarrhea – Increased number of stools for less than 1 week
 - a. Usually infectious
 - b. In children 6 months to 2 years of age, most common cause is acute, infectious etiology (viral most often)
 - i. Viral – More than one-half of pediatric diarrheal illnesses; incubation time of 12 hours to 3 days; present with vomiting, nonbloody diarrhea, abdominal cramping, nausea; seasonal – spring and winter months
 - (a) Rotavirus – Most common worldwide, affects all children by age 5; resolves in 3–7 days
 - (b) Norovirus – 50% of all gastroenteritis outbreaks, leading cause in United States; highly contagious and spread through contaminated food and water; resolves in 12–48 hours
 - (c) Enteric adenoviruses
 - (d) Astrovirus
 - (e) Coronavirus

- ii. Bacterial – Less common; seasonal – Summer months
 - (a) Enterotoxigenic (watery diarrhea) – Self-limiting
 - (b) Dysentery (invasive diarrhea) – Close monitoring required, especially if bloody or pus-containing stools
 - (c) *C. difficile* – Most common cause of nosocomial infectious diarrhea in the United States
 - (1) Gram-positive, spore-forming anaerobic bacillus – Causes toxin-mediated diarrhea
 - (2) Toxin A (enterotoxin) causes fluid and mucus secretion, mucosal damage, and inflammation.
 - (3) Toxin B (cytotoxin) is potent and causes mucosal damage.
 - (4) Varies in severity; if antibiotic-associated, can occur on the first day of antibiotic therapy or even several weeks after completing therapy
 - (5) Diarrhea is watery, but can develop into pseudomembranous colitis and even toxic megacolon, especially with use of loperamide. Loperamide should be held if *C. difficile* positive
 - (6) Children up to 1–2 years of age have a high incidence of positive test results, but they are asymptomatic carriers.
 - (7) Probability of clinically significant disease in non-immunocompromised children up to 5 years of age is low. *C. difficile* infections in the immunocompromised population are clinically significant.
 - (d) Travelers' diarrhea
 - (1) Traveling from industrialized nations to developing countries and ingesting contaminated food or water
 - (2) Common bacteria – Enterotoxigenic *E. coli*, *Campylobacter*, *Salmonella*, *Shigella*
- iii. Parasites – Developing and industrial countries
 - (a) *Giardia lamblia*
 - (b) *Cryptosporidium*
 - (1) Transmitted through recreational water sources or exposure to infected animals (cattle); fecal – oral
 - (2) Oocytes are shed in feces for up to 2 months after diarrhea subsides and are still infectious.
 - (3) Immunocompromised patients can have severe sequelae.
- 4. Chronic diarrhea – Diarrhea lasting more than 14 consecutive days and usually associated with chronic medical conditions
 - a. Malabsorption syndromes (cystic fibrosis, celiac disease)
 - b. Iatrogenic malabsorption (SBS)
 - c. Functional disorder (IBS)
- 5. Nutrition
 - a. Hyperosmolar formula can cause fluid shifts leading to diarrhea.
 - b. Ingestion of irritating foods (nondigestible fibers or insoluble sugar alcohols)
- 6. Enzyme deficiencies/food sensitivities: Lactase deficiency or lactose intolerance – Inability to digest leads to diarrhea
- 7. Food allergies – May illicit GI response on exposure: Cow's milk protein allergy
- 8. Medication induced: Antibiotic-associated diarrhea – Generally resolves in a few days after antibiotic course discontinued

C. Pathophysiology

1. Results when normal functions for maintaining GI tract fluid and electrolyte balance are impaired
2. Water content of fecal material determines whether stools are too liquid or too dry, which affects bowel function; depends on:
 - a. Fluid ingested through diet
 - b. Contribution from intestinal secretions
 - c. Amount reabsorbed by colon
3. Alterations in absorption and secretion of water and electrolytes can change the normal fecal stool electrolyte concentrations.
4. Four classifications of diarrhea
 - a. Secretory diarrhea
 - i. Occurs in response to a stimulating substance increasing the secretion of water into or decreasing the absorption of water and electrolytes from the intestinal lumen
 - ii. Causes: Unabsorbed dietary fat, laxatives, secretin, bacterial toxins, increased bile salts
 - iii. Clinically characterized by large stool volumes with normal electrolyte content
 - b. Osmotic diarrhea
 - i. Occurs when poorly absorbed substances remain in the lumen, creating an osmotic gradient and causing water to be pulled into the lumen
 - ii. Causes: Malabsorption, lactose intolerance, medications (magnesium, lactulose), pancreatic insufficiency
 - iii. Characterized by watery diarrhea
 - iv. If ingested substance is cause, fasting will decrease or eliminate symptoms
 - c. Exudative diarrhea
 - i. Injury occurs to the mucosal lining of the intestinal tract from inflammation or ulceration, leading to loss of mucus, serum proteins, or blood into the lumen. The damaged intestine prevents water and electrolytes from being absorbed, leading to diarrhea.
 - ii. Causes: Inflammatory bowel diseases (IBDs; CD and UC); infectious diarrhea can present similarly
 - iii. Characterized by the large amount of exudates mentioned earlier
 - d. Altered motility
 - i. Multifactorial and can include
 - (a) Reduction in small intestine contact time
 - (b) Bacterial overgrowth
 - (c) Early emptying of the colon
 - ii. Decreased time for normal absorption and secretin processes changes the composition of intestinal contents, which results in osmotic changes leading to diarrhea.
 - iii. Increased transit time can lead to bacterial overgrowth, which may also precipitate diarrhea.
 - iv. Causes: Surgical resection of gut (SBS), medications (erythromycin or metoclopramide)
 - v. Characterized by sporadic and fast peristaltic waves that impair the absorption of water and prematurely move material into the colon

D. Clinical Presentation and Diagnosis

1. Evaluate patient for frequency, volume, color of stool, onset, consistency, medication history, recent travel, drinking water type, diet
2. Origin
 - a. Small intestine – Large amount of watery, foul-smelling stool containing undigested food
 - b. Colon – Diarrhea with red blood
3. Assess hydration status and vital signs: Urinary output, mucus membranes, tear production, physical and mental status changes, sunken fontanelle

4. Physical examination findings
 - a. Abdominal tenderness
 - b. Cramping and/or bloating
 5. Stool studies
 - a. Generally not required unless diarrhea persists longer than 24 hours or a specific diagnosis is needed
 - b. May be helpful for malabsorption or confirmation of infectious etiology
 - c. Fecal leukocytes – Indicate inflammatory response (infectious or IBD); if positive, a stool culture may be warranted
 - d. Stool culture – If infectious cause is suspected (e.g., rotavirus can be diagnosed on the same day as stool sample collection). Stool viral antigens are diagnosed through enzyme immunoassay, latex agglutination assay, or polymerase chain reaction (PCR).
 - e. Antibody serologic tests – Not specific, time-dependent
 - f. Stool examination and/or analysis – Look for presence of ova and parasites, mucus, fat; can also get osmolality, pH, and electrolyte content
 - g. *C. difficile* testing – Rapid enzyme-linked immunosorbent assay (ELISA) (PCR); nucleic acid amplification (NAAT) can also be used as a one-step testing method
- E. Course and Prognosis
1. Acute diarrhea – Generally self-limiting; duration depends on underlying infectious cause
 2. Chronic diarrhea – Can provide symptomatic relief, but must address underlying cause
 - a. Malnutrition – Bidirectional relationship; malnutrition can predispose patient to diarrhea because of increased infection risk; chronic diarrhea is often linked to malabsorptive syndromes, thus causing malnutrition
 - b. Chronic nonspecific diarrhea – “Toddler’s diarrhea”
 - i. Recent use of antibiotics or recent flu-like illness usually precipitates symptoms.
 - ii. Most common between 9 months and 3½ years of age
 - iii. Characterized by 6–8 “runny” stools per day (in an otherwise healthy child)
 - iv. By 3½ years of age, diarrhea is resolved and/or no other diagnosis is made regarding etiology.
 - v. Associated with: Low-fat, high-carbohydrate diets (worse during stress); toddlers drinking a large amount of high-sugar fruit juices, over- or underfeeding, ingestion of irritating foods (tomatoes, citrus)
 - vi. Treat by changing to higher-fat, lower-carbohydrate diet and minimizing sugary drinks.
 3. *C. difficile* infection (Clin Infect Dis 2018;66:e1-e48) (Table 4)

Table 4. Symptoms Related to Severity of *C. difficile* Infection

Mild	A few loose, watery stools per day Abdominal pain Low-grade fever Mild leukocytosis
Colitis	Frequent, watery diarrhea (up to 15 BMs a day) Abdominal pain and distension Nausea Anorexia Fever Leukocytosis

Table 4. Symptoms Related to Severity of *C. difficile* Infection (*continued*)

Fulminant disease	Severe abdominal pain Profuse diarrhea Fever Dehydration Tachycardia Marked leukocytosis Possible hypotension
Toxic megacolon	Acute colonic dilation Signs of systemic disease (e.g., fever, dehydration, abdominal pain, tachycardia, possible hypotension) Cessation of BMs

BM = bowel movement.

- a. High suspicion – Patients with unexplained and new onset of 3 or more unformed stools in 24 hours are considered the preferred target population for testing for *C. difficile* infection. Testing recommendations include the NAAT or the NAAT plus stool toxin; recommendations are for children 2 years and older to have testing if they have prolonged or worsening diarrhea and risk factors starred in the text that follows.
- b. Infants have high colonization rates (up to 50%) but are asymptomatic. At 2 years of age, about 10% of children are still colonized. At 3 years, rates are similar to those in healthy adults. Routine testing in children 1–2 years of age with diarrhea is not recommended.
- c. High risk
 - i. Antibiotics
 - ii. PPIs
 - iii. G- or J-tube
 - iv. Small bowel feeding
 - v. Prolonged hospitalization
 - vi. Proximity to others infected
 - vii. Immunocompromised state
 - viii. Hirschsprung disease
 - ix. IBD
 - x. Infant botulism
 - xi. Cystic fibrosis
- d. Treatment
 - i. Discontinue inciting antibiotics. If antibiotics cannot be discontinued, antimicrobial therapy should be tailored to achieve the narrowest spectrum and shortest duration possible.
 - ii. Depends on disease severity – New guidelines in adult patients remove metronidazole for first-line therapy; however, metronidazole is still an option for nonsevere infections (CID 2018;6:e1-e48).
 - iii. Initial episode in children (nonsevere)
 - (a) Metronidazole
 - (1) Historically, the drug of choice for moderate illness or mild-moderate illness that persists after discontinuing antibiotic therapy
 - (2) Dose: 7.5 mg/kg/dose (max 2 g/day) orally three or four times daily x 10–14 days
 - (b) Vancomycin
 - (1) In adults, now recommended as initial treatment for even mild *C. difficile* rather than metronidazole, citing higher cure rates for vancomycin and fidaxomicin than for metronidazole
 - (2) Dose: 10 mg/kg/dose (max 2 g/day) orally three or four times daily x 10–14 days

- iv. Initial episode, severe/fulminant: Vancomycin 10 mg/kg/dose orally/rectally four times daily x 10 days with or without metronidazole 10 mg/kg/dose intravenously three times daily
- v. First recurrence, nonsevere: Metronidazole 7.5 mg/kg/dose orally three or four times daily x 10 days OR vancomycin 10 mg/kg/dose (max 2 g/day) orally four times daily x 10 days
- vi. Second or subsequent recurrence
 - (a) Vancomycin taper or pulse regimen OR vancomycin 10 mg/kg/dose orally four times daily followed by rifaximin x 20 days OR fecal microbiota transplantation
 - (b) Published tapers vary in dosing changes and total duration (some suggest 7 weeks for taper duration). The American Academy of Pediatrics suggests vancomycin tapers for the second recurrence (third episode) or chronic therapy instead of metronidazole because of concern for neurotoxicity with metronidazole. Guidance on taper dosing and duration is provided in the 2018 guidelines.
- vii. Intravenous metronidazole may be used in children unable to tolerate oral metronidazole; however, one study suggested increased mortality with the intravenous route.
- viii. For an ileus
 - (a) Rectal vancomycin by retention enema in four doses per day (250 mg/50 mL for children 1–3 years of age, 375 mg/75 mL for children 4–9 years of age, and 500 mg/100 mL for those 10 years and older)
 - (b) Therapeutic monitoring, through renal function assessment and drug concentrations, may be warranted with rectal use secondary to an inflamed colon, increasing the risk of toxicity.
- ix. Fidaxomicin
 - (a) Reserved for toxic megacolon and treatment failure after several courses of oral metronidazole and vancomycin
 - (b) The SUNSHINE study compared oral vancomycin with fidaxomicin in pediatric patients with confirmed *C. difficile* infection. Fidaxomicin had significantly higher rates of clinical response without recurrence (adjusted treatment difference of 18.8%). This may suggest using fidaxomicin earlier in treatment and/or prior to oral vancomycin (Clin Infect Dis 2020;71:2581-8).
- x. Fecal microbiota transplantation
 - (a) Stronger recommendations for two or more recurrences of *C. difficile* with previous treatment failure
 - (b) Not FDA approved, but guidance statements have been issued
- xi. Probiotics
 - (a) Used for treatment and prevention of *C. difficile*–associated diarrhea, usually recurrent disease
 - (b) *Saccharomyces boulardii*, *Lactobacillus rhamnosus*, or a combination of *Lactobacillus acidophilus* and *Lactobacillus casei* has the most supporting data.
 - (c) Pediatric data still lacking and no firm recommendations exist for routine use – 2018 guidelines continue to state insufficient data for primary prevention of *C. difficile*
 - (d) Review of adult and pediatric antibiotic-associated and *C. difficile*–associated diarrhea listed probiotics as potential adjunctive therapy (World J Gastroenterol 2016;22:3078-104)
 - (e) Probiotic-related fungemia has been reported; especially at risk are neonates, immunocompromised patients, and patients with central lines.
- 4. Diet – Infant nutrition can be a major player, either acute (osmotic from overfeeding or developmental differences) or chronic (lactose intolerance).
 - a. Neonates have developmental-related deficiency in amylase, which increases the carbohydrate content in the stool.
 - b. Drinks or foods containing a large amount of sorbitol may cause osmotic diarrhea.
 - c. Spicy foods, high-fiber foods, and histamine-containing or releasing foods (tomatoes, cheeses, citrus fruits, fish) may also contribute to diarrhea.

- d. Lactase
 - i. Produced by cells lining the small intestine
 - ii. Older children and adults may become deficient, leading to lactose intolerance; children younger than 2 years have high lactase production and are not typically lactose intolerant.
 - iii. In acute gastroenteritis, the absorptive intestinal lining becomes damaged, causing a transient lactose intolerance.
 - iv. Slow reintroduction of lactose-containing foods may be warranted; formula changes should be discussed with a provider.
- e. Formula versus breast milk
 - i. Breastfed infants have softer stool than do infants on cow's milk formula; if diarrhea is present, infectious causes should be ruled out.
 - ii. Formula, although associated with firmer stools, can cause diarrhea in the presence of a high-calorie or high-sugar content formulas.
 - iii. Empirically changing formulas often is discouraged and should be discussed with the provider first.
- 5. Allergic diarrhea
 - a. Milk protein allergy is most common in infants younger than 1 year, but the overall incidence is only 0.5%–1%.
 - i. Change to an elemental formula, but allergy generally resolves by 12 months of age and can rechallenge. Soy cross-reactions are common and are generally avoided with true milk protein allergy.
 - ii. Breastfeeding mothers should avoid dairy in case of a milk protein allergy.
 - iii. Risk factors: Family history of atopy
 - iv. Clinical symptoms: Flecks of blood in the stool (in an otherwise healthy infant)
 - v. If diarrhea with milk-containing products continues during childhood, other diagnostic work-ups are indicated (e.g., celiac-like disorder).
 - b. Gluten allergy – Gluten, which is protein contained in wheat, rye, and barley, is implicated in intestinal damage in the autoimmune disorder known as celiac disease; gluten avoidance is necessary. (Note: Prevalence of celiac disease in North America is 0.5%.)
 - c. Immunoglobulin (Ig)E-mediated food allergies – Peanut, egg, and fish allergies
 - i. Generally last a lifetime and are not outgrown
 - ii. Allergic responses often involve immediate anaphylactic-type reactions, which may include vomiting, diarrhea, hypotension, and pallor.
- 6. Dehydration risk
 - a. Children younger than 2 years are at greatest risk because water in children constitutes a larger portion of body composition than in adults, and the ability of the kidneys to conserve water is decreased in children.
 - b. Severe dehydration with electrolyte abnormalities may lead to morbidities, including seizures or hypovolemic shock.
 - c. Therapy depends on severity of dehydration and diarrhea (see Fluids, Electrolytes, and Nutrition chapter).

F. Treatment

- 1. Nonpharmacologic therapy – Infectious and noninfectious causes
 - a. Restoring fluid and electrolyte balance
 - i. Cornerstone for managing dehydration associated with diarrhea
 - ii. Oral or intravenous replacement, depending on severity of diarrhea (see Fluids, Electrolytes, and Nutrition chapter)

- b. Temporary dietary modifications during acute illness
 - i. Fasting
 - (a) Usually unnecessary if patient is tolerating eating, but type or quantity of food may need to be modified
 - (b) Guidelines recommend early introduction of appropriate food and liquids during replacement process.
 - (c) However, formula during initial rehydration should be avoided in a formula-fed infant with severe diarrhea.
 - (d) Fasting, clear liquid diets, and BRAT (bananas, rice, applesauce, and toast) diet are not recommended and may prolong diarrhea by preventing cellular repair and generation.
 - ii. Low-residue diet recommended
 - (a) Easily digestible foods
 - (b) No high-fat or high-carbohydrate foods
 - iii. Breastfeeding: Should continue – Has been shown to reduce morbidity and mortality
2. Pharmacologic therapy (Table 5)
 - a. Medications and pharmacologic therapy are generally used for supportive care management of diarrhea.
 - b. Guidelines are still lacking for use of medication in the infant and toddler populations.
 - c. When selecting an agent, balance efficacy and safety.
 - d. Major considerations include etiology and age group.
 - e. Most pharmacologic agents are last line for symptom relief.
 - f. Antidiarrheal agents should be avoided if diarrhea is secondary to any infectious etiology because these agents will prevent the toxin from being cleared.

Table 5. Pharmacologic Therapy for Diarrhea in Children

Category/ Mechanism	Agents	Enteral Dosing	Notes
Opioids Mu-receptor agonist in the GI tract – Delay GI transit time and prolong contact time	Diphenoxylate and atropine	<i>(Dosing expressed in milligram dosing units of morphine)</i> Neonates (usual dose for neonatal abstinence syndrome): 0.08–0.2 mg/dose given q3–4hr (max 0.28 mg) Adults: 3–10 mg/dose of undiluted opium tincture (10 mg/mL morphine) q3–6hr (max 60 mg/24 hr) Neonates (<i>neonatal abstinence dosing</i>): 0.1 mL/kg or 2 drops/kg with feeds q3–4hr (usual max 0.7 mL/dose) Children: 0.25–0.5 mL/kg QD-QID Adults: 5–10 mL QD-QID Children 2–12 yr (as diphenoxylate component): 0.3–0.4 mg/kg/day divided QID Adults: 5 mg QID until control achieved (max 20 mg/day)	Risk of constipation/ileus Studied in both acute and chronic diarrhea – But abuse potential and ileus risk makes them not widely used Historically, the opioids paregoric and tincture of opium were used; paregoric is no longer available in the United States Diphenoxylate/atropine works best when taken before meals/ feedings May be most beneficial for children with malabsorption secondary to SBS (diphenoxylate and atropine)

Table 5. Pharmacologic Therapy for Diarrhea in Children (*continued*)

Category/ Mechanism	Agents	Enteral Dosing	Notes
Opioid derivative Mu-receptor agonist, but does not cross blood-brain barrier, so void of analgesic or other CNS adverse effects Also acts peripherally as antisecretory agent, which regulates chloride secretion	Loperamide	Infants ≥ 2 mo and children: 0.08–0.24 mg/kg/day divided BID-TID; studies have shown doses up to 0.8 mg/kg/day divided BID-TID	Liquid formulation contains sugar and/or alcohol, which may exacerbate diarrhea Avoid in children < 3 yr, malnourished, severely dehydrated, or with bloody diarrhea – At increased risk of adverse events (lethargy, abdominal distension, ileus) Necrotizing enterocolitis has been reported in children < 2 yr Trial for children with SBS to help with malabsorption
Bile acid sequestrant Forms a nonabsorbable complex with bile acids in the intestines and causes the release of chloride ions during this process; chloride ions are absorbed, allowing water to follow	Cholestyramine	240 mg/kg/day divided TID (max daily dose 8 g/day)	Risk of hyperchloremic acidosis If giving with other medications or supplements, agents should be given 1 hr before or 4–6 hr after cholestyramine to prevent binding and decreased absorption Give with plenty of water
Adsorbents/ bulking agents Nonspecific in their action; absorb liquid in GI tract, which alters fluid and electrolyte content and expands the stool (forms “bulk”) Although also used as a laxative, its bulking properties can result in formation of stool and decrease diarrhea	Psyllium	Can target normal fiber intake goals; constipation dosing (may require less per day for diarrhea) Children 6–11 yr: 1.25–15 g/day in divided doses Children ≥ 12 yr and adults: 2.5–30 g/day in divided doses	May absorb medications and nutrients, so should be given 1 hr before or 4–6 hr after psyllium administration Give with plenty of water to avoid constipation and potential obstruction
	Guar gum	4–6 yr: 3 g/day; 6–12 yr: 4 g/day; ≥ 12 –16 yr: 5 g/day	May decrease metformin serum concentrations; abdominal pain, diarrhea, flatulence, GI obstruction have been reported
	Polycarbophil	Children 6–12 yr: 625 mg of calcium polycarbophil one to four times/day; children ≥ 12 yr: see adult dosing	Administer with 8 oz of water or other fluids, administer ≥ 2 hr before or after other medications
	Methylcellulose fiber	Children 6–11 yr: 1 g up to three times/day; children ≥ 12 yr: 2 g up to three times/day	Administer with at least 8 oz of fluid; additional water or other fluid is recommended after the dose(s)

Table 5. Pharmacologic Therapy for Diarrhea in Children (*continued*)

Category/ Mechanism	Agents	Enteral Dosing	Notes
Probiotics Mechanism not well understood, but stimulation of host immune system, create competitive environment for microbial growth, extend antimicrobial action on pathogenic organisms	<i>Lactobacillus</i> spp. <i>Bifidobacterium lactis</i> <i>Streptococcus thermophiles</i> <i>Saccharomyces boulardii</i>	<i>Lactobacillus</i> : Children and adults (oral) [capsules]: 1–2 capsules BID-QID; [granules] 1 packet added to food/water TID-QID; [powder] ¼–1 teaspoon QD-TID with liquid; [chewable tablet] 4 tablets TID-QID <i>S. boulardii</i> Children [pediatric formulation]: 250 mg BID	Most studied – <i>Lactobacillus</i> and <i>Bifidobacterium</i> spp. <i>S. boulardii</i> (nonpathogenic yeast) studied in the treatment of diarrhea, particularly in <i>C. difficile</i> infections Controversy on risk of seeding organism in bloodstream, especially in neonates, immunocompromised patients, or those with a central line
Vitamins/minerals Zinc is an essential mineral that plays a role in immune function and may be lost in stool; may also enhance cation absorption or suppress cation secretion Vitamin A mechanism not well understood	Zinc Vitamin A	<i>Dosing for diarrhea treatment in malnourished patient (WHO/UNICEF, 2004):</i> Infants < 6 mo: 10 mg (elemental zinc) QD for 10–14 days Infants > 6 mo and children: 20 mg (elemental zinc) QD for 10–14 days No clear dosing recommendations, but screen for underlying deficiency and dose accordingly <i>Malabsorption dosing</i> 5000–15,000 units/day of water miscible enteral products (e.g., Aquasaol A); treatment should start on lower end of the dosing range for younger patients	Zinc recommended in developing countries, particularly in children who are malnourished Risk of copper deficiency with long-term zinc (high zinc doses for 10 wk or recommended supplementation for 10 mo and copper deficiency have been reported) Routine use not recommended Vitamin A dosing should be individualized and use serum markers and clinical condition; in geographical areas at-risk for deficiency, the WHO provides specific dosing based on night blindness prevalence
Anti-secretory/anti-inflammatory Facilitates absorption of extra water in the intestine as an antisecretory agent Also inhibits prostaglandins associated with inflammation and possible hypermotility (from hydrolysis to salicylic acid)	Bismuth subsalicylate	Nonspecific diarrhea dosing: Children: 100 mg/kg/day divided into five equal doses for 5 days (max 4.19 g/day) OR 3–6 yr: 1/3 tablet or 5 mL q 30 min to 1 hr as needed* 6–9 yr: 2/3 tablet or 10 mL q 30 min to 1 hr as needed* 9–12 yr: 1 tablet or 15 mL q 30 min to 1 hr as needed* *Up to eight doses in a 24-hour period Chronic infantile diarrhea: 2–24 mo: 2.5 mL (44 mg) q4hr 24–48 mo: 5 mL (87 mg) q4hr 48–70 mo: 10 mL (175 mg) q4hr	All products contain salicylates; use caution in individuals with chickenpox or influenza (risk of Reye syndrome) Can cause stools to turn black Salicylism, characterized by ringing of the ears, nausea, and vomiting, can occur with high intake

CNS = central nervous system.

G. Monitoring

1. Hydration status is most important.
 - a. Determine degree of dehydration.
 - b. Correct deficit and initiate maintenance.
2. Consider trial of oral nutrition, and monitor for response/return of symptoms.
3. Examine body weight (daily) and fluid balance tools (input/output).
4. Serum electrolytes for severe dehydration
5. Infectious – CBC, urinalysis, blood or stool cultures. Prevention is key – Proper hygiene and vaccination, particularly for rotavirus
6. Chronic diarrhea – Focus on underlying cause.

Patient Case

3. A 14-year-old white male adolescent with cystic fibrosis is admitted to the hospital for a second course of intravenous antibiotic therapy in a 1-month period. After 10 days of the current antibiotic therapy, the patient begins to have frequent, watery diarrhea with abdominal pain and some distension. He also has nausea and has had some fevers. Testing is positive for *C. difficile*. This is this patient's first episode of *C. difficile*. Which is the best initial therapy for him?
 - A. Discontinue antibiotic therapy.
 - B. Initiate metronidazole 30 mg/kg/day intravenously divided every 6 hours.
 - C. Initiate vancomycin 40 mg/kg/day orally divided every 6 hours.
 - D. Initiate fidaxomicin 200 mg orally twice daily.

III. CONSTIPATION

A. Definition

1. New NASPGHAN guidelines still use Rome III criteria (J Pediatr Gastroenterol Nutr 2014;58:258-74) (Table 6). Rome IV criteria have been updated to match NASPGHAN and ESPGHAN suggestions for quicker attention to symptoms (1 month instead of 2 months).
2. Challenging because of a differing definition of “normal” – Will vary from patient to patient
3. Having less than 3 BMs per week, hard stools; has excessive straining or a feeling of incomplete evacuation

Table 6. Rome IV Criteria (2016) Definitions for Functional Constipation

Infants and toddlers (up to 4 yr)	1 mo of ≥ 2 of the following: 1. ≤ 2 defecations per week 2. History of excessive stool retentions 3. History of painful or hard BMs 4. History of large-diameter stools 5. Presence of a large fecal mass in the rectum In toilet-trained children, additional criteria may be used: 1. At least one episode per week of incontinence after learning toileting skills 2. History of large-diameter stools that may obstruct the toilet

Table 6. Rome IV Criteria (2016) Definitions for Functional Constipation (*continued*)

Children > 4 yr and adolescents	≥ 2 of the following six criteria occurring at least once per week for at least 1 mo – Children at least 4 yr of age, not meeting the criteria for IBS 1. ≤ 2 defecations in the toilet per week in a child of developmental age of at least 4 yr 2. At least one episode of fecal incontinence per week 3. History of retentive posturing or excessive volitional stool retention 4. History of painful or hard BMs 5. Presence of a large fecal mass in the rectum 6. History of large-diameter stools that can obstruct the toilet

IBS = irritable bowel syndrome.

4. Risk factors: Children with birth weight less than 750 g and in the presence of neurodevelopmental impairments; low-fiber diet; obesity; sedentary lifestyle

B. Etiology

1. Anatomic/organic
 - a. Neurologic (spina bifida, cerebral palsy)
 - b. Hirschsprung disease (highly suggested when symptoms, including delay [more than 48 hours] of meconium passage, are present in patients younger than 1 month)
 - c. Chronic intestinal pseudo-obstruction (neoplasm/malignancy)
 - d. Neuronal intestinal dysplasia
 - e. Connective tissue disorders (systemic lupus erythematosus, scleroderma)
 - f. Metabolic and endocrine disorders (hypothyroidism, diabetes mellitus, hypercalcemia, cystic fibrosis)
2. Diet
 - a. Low-fiber diets
 - b. Dehydration
 - c. Underfeeding infants

3. Medications: Abuse of cathartics can lead to constipation (Box 1).

Box 1. Medications Known to Cause Constipation

Antidepressants/Antipsychotics • Amitriptyline • Nortriptyline • Doxepin • Haloperidol • Risperidone • Olanzapine • Clozapine • Chlorpromazine Antihypertensives/Antiarrhythmics • Calcium channel blockers • Clonidine	Anticholinergics/Antispasmodics • Bromocriptine • Trihexyphenidyl • Benzotropine Opioids Iron-Containing Products • Ferrous sulfate • Ferrous gluconate Antihistamines • Chlorpheniramine • Diphenhydramine • Cetirizine Other • Cholestyramine • Loperamide • Sucralfate

4. Psychogenic
- Traumatic (e.g., abuse)
 - Nontraumatic (e.g., potty training)

C. Clinical Presentation and Diagnosis

- Signs and symptoms
 - Painful passage of stools with hard consistency
 - May have nausea, abdominal pain, distension, bloating
 - “Alarm signs”: See Box 2.

Box 2. Alarm Signs Leading to Potential Underlying Etiology of Constipation

Constipation occurring < 1 mo of age Delayed (> 48 hr) meconium passage Family history of Hirschsprung disease Ribbon stools Bloody stools without anal fissure Fever Bilious vomiting Severe abdominal distension Thyroid gland abnormalities Anal abnormalities (position, fistula, scarring) Decreased lower extremity tone/strength Tuft or hair on spine Sacral dimple Gluteal cleft deviation

- Age at onset may help differentiate underlying cause. NASPGHAN 2014 guidelines show algorithm for patients both younger and older than 6 months.

3. Complications
 - a. Rectal fissures
 - b. Ulcers
 - c. Rectal prolapse
 - d. UTIs
 - e. Incontinence (both fecal [e.g., encopresis] and urinary)
 - f. Impaction/obstruction
 4. Diagnosis
 - a. Involves evaluation of change from normal bowel pattern and if there is complete evacuation of the large colon
 - b. For functional constipation, the child may have certain behaviors that allow suppression of the urge to defecate – Rocking back and forth, standing on tiptoes, or becoming fidgety. Withholding can lead to painful stooling and decreased appetite because of a full colon.
 - c. History
 - i. Stool history with signs/symptoms – Include changes in the stool pattern, duration of absence of BM, size, number, consistency, frequency, pain, bleeding, behaviors, bloating, decreased appetite, urinary tract symptoms, weight changes, dietary changes
 - ii. Use of Bristol Stool Form Scale (see IBS section), Amsterdam infant stool scale, Lane scale
 - d. Physical examination
 - i. Abdominal distension
 - ii. Tenderness
 - iii. Presence of hard stool – Digital rectal examination
 - iv. Physical defects that may support an underlying cause
 - v. Presence of impaction
 - e. Radiographic studies
 - i. Abdominal radiography
 - ii. Barium enema – Useful when diagnosing strictures, abnormal bowel shape, Hirschsprung disease
 - f. Biopsy – Evaluate for Hirschsprung disease.
 - g. Laboratory testing – Helps identify an underlying cause
 - i. Thyroid
 - ii. Magnesium
 - iii. Urinalysis
- D. Treatment
1. Goals of therapy
 - a. Prevention
 - b. Alleviation of acute symptoms
 - c. Management plan to avoid recurrence
 2. Nonpharmacologic therapy
 - a. Contributes largely to the prevention and maintenance plans
 - b. Dietary changes
 - i. Increase fluids: Water, but also sorbitol-containing fruit juices (prune, pear, apple)
 - ii. Increase fiber intake
 - iii. Balanced diet of whole grains, fruits, and vegetables: Avoid constipating foods (dairy, starches).
 - iv. Corn syrup or sorbitol – Osmotic laxative, has been used in infants, generally not recommended
 - c. Behavioral management
 - i. Regular toilet habits (unhurried time on the toilet and maintaining a record of stool frequency)
 - ii. Positive reinforcement system

- d. Digital disimpaction: Not recommended in the primary care setting, but may be useful if other therapies are unsuccessful
3. Pharmacologic therapy (Table 7)
 - a. Use nonpharmacologic therapy with pharmacologic therapy for improved success.
 - b. Disimpaction phase – If fecal impaction present
 - i. Show results within 2–5 days
 - ii. About 50% of children do not have results with initial treatment and require refractory treatment.
 - iii. Oral and rectal routes can be used. In infants, use caution with enema administration to avoid damage to the rectal wall (usually not first line for this population).

Table 7. Guideline Recommendations for Initial (disimpaction) and Maintenance Constipation Therapy

Recommendations for Initial Disimpaction	
First line: PEG ($\pm$ electrolytes)	1–1.5 g/kg/day for 3–6 days
Alternative: Enema	Daily for 3–6 days if PEG not available
Recommendations for Maintenance Therapy	
First line: PEG ($\pm$ electrolytes) (addition of enemas is not recommended)	0.2–0.8 g/kg/day and titrate to response; continue for at least 2 mo; symptoms should be resolved at least 1 mo before treatment discontinuation (if during toilet training phase, continue medication until phase completed)
Alternative first line: Lactulose (if PEG not available)	1–2 g/kg/day, divided daily-BID
Second line (or additional therapy): Milk of magnesia Mineral oil (PO) Stimulant laxatives (bisacodyl, senna, occasional glycerin)	According to Lexi-Comp dosing (<i>also see Table 8</i>): Milk of magnesia (regular strength 400 mg/5 mL): < 2 yr: 0.5 mL/kg/dose 2–5 yr: 5–15 mL/day, once before bedtime or in divided doses 6–11 yr: 15–30 mL/day, once before bedtime or in divided doses $\geq$ 12 yr and adults: 30–60 mL/day, once before bedtime or in divided doses Mineral oil (PO): 1–18 yr: 1–3 mL/kg/day, once or divided (max 90 mL/day)
Refractory therapy: Use of contrast enemas only recommended for intractable constipation Use of nerve stimulation not recommended	

PEG = polyethylene glycol.

Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. *J Pediatr Gastroenterol Nutr* 2014;58:258-74.

- c. Maintenance phase – Requires 3–12 months to sustain results
- d. See Table 8 for therapy comparisons and special notes.
- e. Osmotic laxatives
- f. Stimulant laxatives – Good for fecal impaction

- g. Combinations for maintenance therapy
 - i. Lubricants, osmotic laxatives
 - ii. Infants – Stool softener alone
 - iii. Toddlers – Stool softener and stimulants (because of stool-withholding behaviors)
- h. Routine use of lubiprostone, linaclotide, and prucalopride in children with intractable constipation is not recommended.

Table 8. Pharmacologic Therapy for Constipation

Agent	Dosing	Onset	Comments
Stool Softeners			
Docusate salts (same dosing for sodium, calcium, potassium salts)	< 3 yr: 10–40 mg/day in one to four divided doses 3–6 yr: 20–60 mg/day in one to four divided doses 6–12 yr: 40–150 mg/day in one to four divided doses > 12 yr and adults: 50–400 mg/day in one to four divided doses	12–72 hr	Useful in prevention of constipation, not as sole agent for treatment of impaction
Lubricant			
Mineral oil	Rapid disimpaction: 15–30 mL per year of age (max 240 mL/day) as a single dose Slow disimpaction: 3 mL/kg BID x 7 days Maintenance: PO: 5–11 yr: 5–15 mL once daily or divided (max dose 15 mL/day) > 12 yr: 12–45 mL/day once or in divided doses (max dose 45 mL/day) Rectal: 2–11 yr: 30–60 mL as a single dose > 12 yr: 50–150 mL as a single dose	6–8 hr	Should not be used for > 1 wk; caution with use in children < 5 yr because of risk of aspiration Titrate to effect to avoid anal leakage
Osmotic Laxatives			
Polyethylene glycol (PEG)	MiraLAX PO: Child < 20 kg (limited data; studied in children 18 mo to 11 yr for chronic constipation): 0.25–1 g/kg/day PO divided BID (max 17 g/day) > 20 kg: 17 g in 240 mL of water daily GoLYTELY PO: Maintenance: 5–10 mL/kg/day	At constipation dosing, results can occur after 2 days to 1 wk of therapy	Contraindicated in bowel obstruction; monitor for electrolyte disturbances Safety of long-term use has not been well established

Table 8. Pharmacologic Therapy for Constipation (*continued*)

Agent	Dosing	Onset	Comments
Lactulose	Children: 1–3 mL/kg/day in divided doses, max daily dose 60 mL/day Adults: 15–30 mL/day to a max of 60 mL/day	Within 24 hr	Indigestible sugar; well tolerated for long-term use, but limited data on disimpaction Flatulence and cramping common After therapy discontinuation, allow 24–48 hr before normal bowel function resumes
Sorbitol	PO as 70% solution: Children: 1–3 mL/kg/day in divided doses (usually BID) Adults: 30–150 mL as single dose Enema: 120 mL as a single dose (25–30% solution)	Within 24 hr	Indigestible sugar; limited data on disimpaction Flatulence and some abdominal cramping Adjust dose on the basis of the number of daily BMs (lactulose and sorbitol similar)
Magnesium citrate	< 6 yr: 2–4 mL/kg/dose given once or in divided doses 6–12 yr: 100–150 mL/dose given once or in divided doses > 12 yr: 150–300 mL/dose given once or in divided doses	A few hours after PO administration	Used for acute evacuation, not impaction Not used in children < 2 yr because of the risk of magnesium toxicity; cramping, gas
Magnesium hydroxide	(All liquid milliliter doses are based on 400 mg/5 mL of magnesium hydroxide unless noted otherwise): < 2 yr: 0.5 mL/kg/dose 2–5 yr: 5–15 mL or 311–622 mg (1 or 2 chewable tablets) 6–11 yr: 15–30 mL or 933–1244 mg (3 or 4 chewable tablets) > 12 yr and adults: 30–60 mL or 1866–2488 mg (6–8 chewable tablets)	0.5–6 hr	Use with caution in patients with renal impairment More for maintenance therapy; not for use in infants because of magnesium toxicity; cramping, gas
Phosphate soda enema	Enema: 2–4 yr: ½ pediatric enema 5–11 yr: 1 pediatric enema > 12 yr and adults: 133 mL enema x 1; may repeat x 1 PO: 5–9 yr: 5 mL PO x 1 dose 10–12 yr: 10 mL PO x 1 dose > 12 yr and adults: 20–30 mL PO x 1 dose	Rectal: 2–5 min PO: 3–6 hr	Reserved for children > 2 yr For PO administration, mix 1:1 with water. Separate doses by 10–12 hr Contraindicated in renal failure. May cause electrolyte disturbances

Table 8. Pharmacologic Therapy for Constipation (*continued*)

Agent	Dosing	Onset	Comments
Stimulant Laxatives			
Bisacodyl	PO: 3–12 yr: 5–10 mg or 0.3 mg/kg/day as a single dose (max 30 mg/day) > 12 yr: 5–15 mg/day as a single dose (max 30 mg/day) Rectal: < 2 yr: 5 mg/day as a single dose 2–11 yr: 5–10 mg/day as a single dose > 12: 10 mg/day as a single dose	PO: 6–10 hr Rectal: 15–60 min	PO may have better efficacy for disimpaction because rectal will be inserted in the middle of the stool and will not come in contact with the mucosa (desired site of action) Not recommended for daily use; may cause considerable abdominal cramping, hypokalemia, diarrhea
Sennosides	Syrup (8.8 mg/5 mL) 1 mo to 2 yr: 1.25–2.5 mL HS (max 5 mL) 2–6 yr: 2.5–3.75 mL HS (max 3.75 mL) 6–12 yr: 5–7.5 mL HS (max 7.5 mL) > 12 yr: 10–15 mL HS (max 15 mL) Tablet (8.6 mg): 2–6 yr: ½ tablet HS (max 1 tablet BID) 6–12 yr: 1 tablet (max 2 tablets BID) > 12 yr: 2 tablets (max 4 tablets BID)	PO: Within 6–24 hr Rectal: Evacuation occurs in 30 min to 2 hr	Often used in combination with stool softeners – Docusate enhances the absorption of senna Melanosis coli (benign darkening of the colon that improves within 4–12 mo after senna discontinuation)
Glycerin	Neonates: ½ glycerin suppository as needed Children: < 6 yr: 1 infant suppository as needed > 6 yr: 1 adult suppository as needed	15–30 min	Most widely used in neonatal and infant populations; effectiveness may decrease if rectal distension has occurred Not useful for impaction; considered a safe laxative

E. Monitoring/Follow-Up

1. Disimpaction must occur first – If it does not occur with therapy, hospital admission for oral gastric lavage is necessary.
2. Maintenance phase – Can take 2–6 months, so must evaluate for dependence on stimulants or laxatives
3. Weaning of therapy can occur – Gradual withdrawal of therapy and only after normal function has returned. May wean to every other day if receiving daily therapy; then every 3 days (for 1-month periods) until complete evacuation daily
4. May need to give stimulant if child does not stool for more than 3 days

Patient Case

4. An 8-year-old boy with constipation is not adhering to his laxative regimen and has fecal impaction. Which is the best treatment for stool evacuation?
- A. Bisacodyl suppositories.
 - B. Oral magnesium hydroxide.
 - C. Oral polyethylene glycol.
 - D. Contrast enema.

IV. IRRITABLE BOWEL SYNDROME**A. Definition**

1. IBS – (ROME IV committee definition): A chronic disorder characterized by abdominal pain associated with disordered defecation (constipation [IBS-C], diarrhea [IBS-D], or mixed/alternating symptoms of constipation and diarrhea [IBS-M]); does not damage the intestinal tract
Bristol Stool Form Scale:
 - a. IBS-C: 25% or more of BMs: hard or lumpy stools; 25% or less of BMs: loose/mushy or watery stools (types 1 and 2)
 - b. IBS-D: 25% or more of BMs: loose/mushy or watery stools; 25% or less of BMs: hard or lumpy stools (types 6 and 7)
 - c. IBS-M: 25% or more of BMs: hard or lumpy stools (types 1 and 2); 25% or more of BMs: loose/mushy or watery stools (types 6 and 7); may also be called “unspecified”
 - d. IBS-U: Those without a significant pattern of abnormal stool cannot be determined.
2. Chronic or recurrent abdominal pain – Symptoms of abdominal pain (without a determined cause) will occur over 3 months.

B. Epidemiology

1. One of the most prevalent GI disorders and a source of reduction in quality of life and increased health care costs
 - a. Girls and boys are affected equally.
 - b. 6% of middle school students, 14% of high school students
2. A collection of symptoms, including stool frequency and consistency changes and abdominal pain. Abdominal pain is the most common symptom in children.
3. Pediatric criteria for IBS classify the patient with recurrent abdominal pain as having functional abdominal pain (35%) or IBS (65%).

C. Pathophysiology

1. Multifactorial, biopsychosocial disorder:
 - a. Altered motility – Increase in frequency of small bowel contractions causing abdominal pain with altered GI transit times. Transit time increased with IBS-D and decreased with IBS-C
 - b. Altered sensation of the intestine (visceral hypersensitivity)
 - i. Feature in most patients with IBS
 - ii. Distension of the lumen of the gut produces pain in IBS from an alteration in communication between the enteric nerves of the intestine and the gut bacteria and the central nervous system (CNS)

- iii. Described as a heightened awareness of sensations that can be perceived as painful – Triggered by bowel distension and bloating (children without IBS would not have the same response or hyperawareness)
 - c. Psychosocial factors
 - i. IBS is associated with a higher incidence of anxiety and depression.
 - ii. Cause of IBS can be difficult to distinguish: Illness with pain-induced anxiety or underlying stress/anxiety
 - 2. Most studies present the following factors as mechanisms for onset:
 - a. Chronic stress
 - b. Genetics: Studies have shown positive family history, identical twins, as predictors
 - c. Serotonin disorders
 - i. Serotonin plays a role in GI motility, sensation, and secretion.
 - ii. Serotonin concentrations differ in patients with IBS-D (increased) and IBS-C (decreased).
 - d. Bacterial overgrowth: Gut flora is altered in patients with IBS.
 - e. Postinfectious (prior bacterial gastroenteritis, 5%–10% of patients develop IBS, predominantly IBS-D)
 - i. Symptoms can last several years after infection resolution.
 - ii. Inflammation and mast cells may also play a role. Some studies show the patients with IBS have an increased number of mast cells.
- D. Diagnosis
- 1. Involves both altered BMs and pain
 - a. Pain is periumbilical and lasts for less than 1 hour; unrelated to meals, activity, or stooling patterns
 - b. Age-dependent pain symptoms (generally not diagnosed in children younger than 4 years secondary to inability to report symptoms)
 - i. 3–10 years – “Belly pain”
 - ii. 11–17 years – Headache, abdominal pain, and back pain
 - 2. Thorough history and physical examination should be obtained because diagnosis is symptom based (no laboratory test or physical marker is used to diagnose IBS).
 - a. Nutritional assessment
 - b. Psychosocial (child and family)
 - c. Evaluate for other causes of abdominal pain (constipation, GERD, ulcers, infections, UTIs, IBD, carbohydrate malabsorption, lactose intolerance, muscle pain, bone pain, menstrual or reproductive disorder).
 - 3. Diagnostic criteria
 - a. The Rome IV criteria add duration and frequency of stools and symptoms (Table 9).
 - b. American College of Gastroenterology (ACG) IBS Task Force also stipulates that further diagnostic testing and colonoscopy should not be done unless the patient has alarm symptoms (Am J Gastroenterol 2009;104(suppl 1):S1-35)
 - i. Alarm symptoms:
 - (a) Unintentional weight loss (more than 10% of ideal body weight in adults, or abnormal weight loss in children)
 - (b) GI bleeding
 - (c) Anemia
 - (d) Recurrent nausea and vomiting
 - (e) Family history (first-degree relative) of GI malignancy or IBD
 - ii. Testing may also help exclude organic causes/differential diagnosis.

Table 9. Diagnostic Criteria for IBS Diagnosis

Committee on Childhood Gastrointestinal Disorders^a	Manning Criteria^b	Rome IV Criteria^c
12 consecutive or nonconsecutive wk in the past 12 mo of abdominal pain with two of the following features: • Pain relieved by defecation • Onset associated with change in stool frequency • Onset associated with change in stool appearance - Absence of structural or metabolic abnormalities that could explain the symptoms	- Presence of abdominal pain <i>plus</i> - Two or more of the following symptoms: • Pain relieved by defecation • More frequent stools at onset of pain • Looser stools at onset of pain • Visible abdominal distension • Passage of mucus • Sensation of incomplete evacuation	- Recurrent abdominal pain at least 4 days/mo in the past 2 mo with one or more of the following: • Related to defecation • Onset associated with a change in stool frequency • Onset associated with a change in stool form (appearance) - Pain does not resolve with resolution of the constipation - Subclassification of IBS (C, D, or M) based on the following symptoms at least 1/4 of occasions (Bristol Stool Form Scale): • Abnormal stool frequency • Abnormal stool form • Abnormal stool passage (straining, incomplete evacuation) • Bloating or feeling of abdominal distension • Passage of mucus • Frequent, loose stools

^aRasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut* 1999;45(suppl II):II60-8; Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006;130:1527-37.

^bManning AP, Thompson WG, Heaton KW, et al. Towards a positive diagnosis of irritable bowel. *Br Med J* 1978;2:653-4.

^cDrossman DA, Corazziari E, Delvaux M, et al. Rome III: The Functional Gastrointestinal Disorders, 3rd ed. McLean, VA: Degnon Associates, 2006:appendix A, 858-98; Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006;130:1480-91.

E. Treatment

- Depends on the severity of symptoms, which symptoms are predominant, and patient factors: Bristol Stool Form Scale used to categorize predominant symptoms (tool used to describe both diarrhea- and constipation-stool characteristics)
- Goals
 - Return to normal bowel function.
 - Eliminate symptoms.
 - Prevent complications (unnecessary surgery, risky diagnostic procedures, adverse effects from polypharmacy, unfavorable impact on quality of life).

3. Nonpharmacologic
 - a. Stress management/cognitive behavioral therapy – American Academy of Pediatrics recommends the following therapies, which can be useful for reducing pain (in 70%–90% of children):
 - i. Relaxation and distraction strategies
 - ii. Diary of symptoms, triggers, and feelings
 - iii. Positive/negative reinforcement
 - b. Dietary changes
 - i. ACG does not recommend food avoidance (except for clinical trials).
 - ii. Lactose intolerance – Children with lactose intolerance have a higher incidence of IBS.
 - (a) Avoid milk and milk-containing products.
 - (b) Use lactase enzyme replacements (according to Lexi-Comp dosing: 1 or 2 capsules taken with milk or meal OR 1–3 tablets with meals).
 - (c) Keep food diary to correctly link symptoms to dairy products at or around the time of IBS symptoms.
 - iii. Avoiding high-fat foods, gas-producing foods, caffeine, and medications (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]) that may aggravate symptoms may be helpful.
 - iv. Gluten avoidance – Helpful if patient has celiac markers present and IBS-D. Celiac-associated serum IgG and *HLA-DQ2* allele expression
 - v. Monitor for weight loss (especially with IBS-D) and malabsorption.
 - (a) Enteral feeding or PN may be warranted for adequate growth or for regaining lost weight.
 - (b) Special attention to zinc, vitamin A, folic acid, copper, and selenium – Supplementation may be needed.
4. Pharmacologic therapy
 - a. IBS-D – Antidiarrheal agents
 - i. Loperamide – Studies of patients with IBD show decreased stool frequency and consistency improved, no improvement in abdominal pain or bloating; short-term use only
 - ii. Diphenoxylate/atropine – No randomized, placebo-controlled trials have been completed in IBS; not recommended
 - iii. Cholestyramine – Not formally studied in IBS, but has been used for patients with chronic diarrhea secondary to bile salt malabsorption
 - b. IBS-C
 - i. Fiber or bulking agents
 - (a) Although not shown in clinical studies, increasing the intake of dietary fiber may improve symptoms (not quality of life).
 - (b) Helps stool hold onto water, bulks and lubricates stool, binds bile
 - (c) Can gradually increase fiber intake to produce more regular BMs; can decrease pain from hardened stools as well as decrease adverse effects of bloating and flatulence
 - (d) Psyllium – Soluble fiber; first-line treatment for IBS-C
 - (1) Powder form – Mixed in drinks, juices
 - (2) Give twice daily with 8 oz of liquid (alternative: 2–4 glasses for younger children and at least 6 glasses for older children).
 - (3) Separate 2 hours from other medications.
 - (4) Avoid in children who have chronic constipation or who withhold.
 - ii. Laxatives
 - (a) Although commonly used in chronic constipation, osmotic and stimulant laxatives have little proven efficacy in IBS studies.
 - (b) Goal is to achieve 1 soft stool per day.
 - (c) In combination with behavioral therapy, may take weeks, months, and years to work

- (d) No relief of abdominal pain in IBS in studies when used in combination with tegaserod (Rome III: The Functional Gastrointestinal Disorders 2006:appendix A, 858-98)
- (e) Initial use with bisacodyl suppositories for intestinal cleansing; then polyethylene glycol 17 g in 8 oz of water daily 1–2 hours before the evening meal
- (f) In addition to efficacy (similar among all laxatives), choice will depend on child preference, administration ease, and cost.
- (g) Adverse effects – See Table 8.
- iii. Lubiprostone – Chloride channel activator leading to increased intestinal motility by stimulating intestinal fluid secretion
 - (a) Currently approved for use in women 18 years and older
 - (b) Study of children and adolescents weighing more than 12 kg for the treatment of functional constipation showing doubling of spontaneous BMs after 4 weeks of treatment; also reduced straining and pain, improved consistency of stool, and reduced laxative use for rescue therapy
- iv. Tegaserod – Selective serotonin-4 receptor partial agonist
 - (a) Was used for adults with IBS-C but was removed from market in 2007 for cardiovascular risks; however, is available by U.S. Food and Drug Administration (FDA) emergency drug protocol for patients younger than 55 years. Risks associated with preexisting cardiovascular disease
 - (b) Increases intestinal peristalsis, decreases visceral hypersensitivity
 - (c) In adolescents, decreases pain associated with IBS when used as a laxative
 - (1) Improved bloating, pain, constipation scores without adverse effects
 - (2) Need randomized controlled trials in this population
- c. Abdominal pain associated with IBS
 - i. Antispasmodics
 - (a) Activation of cholinergic receptors in smooth muscle associated with abdominal pain as well as smooth muscle spasms
 - (b) More studies in adult population, few data in pediatric population
 - (c) Hyoscyamine and dicyclomine – Used for short-term relief; long-term use can lead to the anticholinergic adverse effects of urinary retention, constipation, tachycardia, drowsiness, dry mouth
 - (d) Peppermint oil, menthol – Calcium channel blockade decreases smooth muscle spasms in ileum and colon; reports of efficacy include improvements in symptoms, but not in stool pattern or consistency
 - (e) ACG IBS Task Force recommends short-term use only until long-term efficacy and safety have been shown.
 - ii. Antidepressants – May be best for children with anxiety or other psychological disease states, but overall efficacy and safety data in children are still under investigation
 - (a) Tricyclic antidepressants – Anticholinergic effects decrease pain perception, improve sleep, modulate GI tract
 - (1) Worsen constipation in patients with IBS and constipation, but useful for IBS-D
 - (2) Adverse effects increase as dose is increased (dry mouth, dry eyes, sedation, urinary retention, visual changes); potential cardiac arrhythmias, risk of overdose may limit use
 - (3) Nortriptyline and desipramine – Better tolerated than parent tertiary amine compounds (amitriptyline) secondary to lower anticholinergic, antihistaminic, and α -adrenergic adverse effects

- (4) Pediatric studies of amitriptyline doses of 10, 20, or 30 mg based on weight compared with placebo for 4–8 weeks improved quality of life from baseline and reduced anxiety scores in patients with IBS
 - (5) Use of these agents will depend on a child's ability to tolerate adverse effects.
- (b) SSRIs (selective serotonin reuptake inhibitors) – Serotonin is involved in regulating GI motility and visceral pain; more than 80% of serotonin receptors in the body are in the GI tract.
 - (1) Used in IBS-C secondary to the adverse effect of diarrhea
 - (2) Fluoxetine, paroxetine, and citalopram studied – Citalopram study of pediatric recurrent abdominal pain showed improvement in abdominal pain, anxiety, depression, and daily function in 84% of children.
- iii. Anti-inflammatory agents – Utility based on theory of inflammation involvement in pathogenesis of IBS; existing evidence in adults
 - (a) Prednisolone – Studied in patients post-infection and resulted in no difference in symptoms
 - (b) Mesalamine – Inhibits mast cells in the GI tract and improves overall IBS symptoms, but no difference in abdominal pain or change in bowel habits
- iv. Probiotics – Imbalance in gut flora has been linked to motility dysfunction and visceral hypersensitivity; probiotics may help restore balance.
 - (a) Studies in the pediatric population have shown moderate benefit in decreasing pain but no decrease in the frequency of pain.
 - (b) Most beneficial probiotic strain has not been identified, but most used are *Lactobacillus* products (*E. coli* strain also studied and was well tolerated with fewer adverse events)
 - (c) May take more than 1 month to see benefit
 - (d) Associated with flatulence
- v. Fecal transplantation
 - (a) Fecal transplantation has been used to treat, and even cure, adult patients with IBS and IBD.
 - (b) In a recent study, 13 patients underwent a fecal transplant for refractory IBS (9 of 13 patients had IBS-D) and had a 70% improvement or resolution in symptoms. Of those reporting improvement, 72% had improvement in abdominal pain, 69% in bowel habits, 67% in dyspepsia, 50% in bloating, and 42% in flatus. Overall quality of life was improved in 46% of patients.
 - (c) Currently, fecal transplantation is not approved for IBS in adult or pediatric patients, but more studies may indicate its use in the future for refractory cases.

F. Monitoring

- 1. Related to quality of life
 - a. Treatment should be tailored to the patient's symptoms.
 - b. Dietary changes can be made, but they should be made with optimal nutrition in mind – Monitor growth (weight, height)
- 2. Medication selection should be based on IBS classification and tailored to achieve 1 soft BM per day.
- 3. Monitor for worsening symptoms (abdominal distension or worsening pain).

Patient Case

Questions 5 and 6 pertain to the following case.

A 14-year-old presents with a 6-month history of abdominal pain, headache, and occasional back pain. These symptoms occur before stooling, and when stooling occurs, it is soft and mushy. No constipation has been reported during this time. The episodes have been occurring about five times a month. Dietary changes, involving avoidance of milk and caffeine, have not improved symptoms.

5. Which best describes this patient's IBS classification?
 - A. IBS-C.
 - B. IBS-D.
 - C. IBS-M.
 - D. Patient does not meet the diagnostic criteria for IBS.
6. Which best describes the optimal treatment option for this patient?
 - A. Initiate a trial of a gluten-free diet.
 - B. Give ibuprofen.
 - C. Give fluoxetine.
 - D. Give amitriptyline.

V. INFLAMMATORY BOWEL DISEASE

- A. Epidemiology: 70–150 cases per 100,000 individuals
- B. Background/Classification (Table 10)
 1. IBD is a chronic inflammatory disorder that includes UC and CD and is characterized by abdominal pain, rectal bleeding, weight loss, and diarrhea. Patients who cannot be characterized into one of these two groups or with uncertainty are considered to have indeterminate colitis (IC). Overuse of the IC classification leads to concerns with therapeutic options, ineligibility for clinical trials, and concerns with long-term prognosis.
 2. Perianal CD (PCD) is defined as inflammation at or near the anus, with symptoms including pain, itching, bleeding, purulent discharge, and incontinence of stool.
 3. Potential causes
 - a. Genetic predisposition and microbiota influence the development of perianal fistulae and abscesses (linked to specific gene variants at the susceptibility locus on chromosome 5q31 [IBD5], including *OCTN* and *IRGM*).
 - b. No known primary organism as cause but many implicated in inflammation (enteroadherent strains of *E. coli*, chlamydia, and mycobacteria). It is unclear whether changes in bacterial flora are primary or secondary to disease.
 4. Adult and pediatric presentations have similar clinical features, whereas the genetic component is more dominant with pediatric-onset CD.
 - a. Heightened impact of dynamic physical changes, bone growth, and emotional maturation in the pediatric population
 - b. More extensive and aggressive course requiring immunomodulators sooner than in adults
 5. Newer classification of very early onset IBD (VEO-IBD) exists. Patients younger than 5 years of age present with symptoms outside of the “classic” symptoms listed in this chapter. Patients with VEO-IBD do not respond to traditional treatments and would require specialist evaluation.

6. Predictive factors for poor outcomes: Deep colonic ulcerations on endoscopy, persistent severe disease despite adequate induction therapy, extensive (pan-enteric disease), marked growth retardation (greater than -2.5 height z-scores), severe osteoporosis, stricturing and penetrating disease at onset, severe perianal disease
7. Additional considerations: Patients with IBD and central venous catheters are at increased risk of thrombotic events and warrant anticoagulation prophylaxis evaluation

Table 10. Differentiation Between CD and UC

Features	Crohn Disease	Ulcerative Colitis
Physical examination	Perianal fistula Abscess Large (> 5 mm) skin tags	No fistulas, strictures, or perforations May have small anal fissures or skin tags (“non-classic feature”)
Imaging	Small bowel involvement Mucosal ulceration Cobblestone appearance Narrowing/obstruction Enteric fistula	Continuous inflammation, but superficial
Colonoscopy findings	Ulceration and stenosis of ileocecal valve Cobblestoning in the ileum Stricture and fistula formation	Diffuse, continuous process starting at rectum extending into colon; may have backwash ileitis (inflammation in the distal ileum) Continuous edema, erythema, ulceration
Histology	Noncaseating granulomas (unless adjacent to ruptured cysts) Inflammation is transmural	Mucosal and submucosal inflammation, crypt abscess formation
Bowel involvement	Upper and lower GI (mostly ileum)	Rectum and colon
Other features	Malabsorption, vitamin deficiencies, growth restriction	Development of toxic megacolon, pseudopolyps

C. Presentation/Clinical Findings of PCD

1. PCD can be surprisingly painless, so it is important to ask direct questions.
 - a. Anal skin tags a cosmetic concern, but often painless unless inflamed
 - b. Functional impairments (constipation, incontinence, spontaneous drainage) and social implications (odor, stained undergarments, anxiety) often significant
2. Strictures are typically a result of long-standing inflammation (slow forming), allowing accommodation to relative narrowing of rectum (often affording ability to pass stools despite rectal strictures).

D. CD Treatment

1. Goals/principles
 - a. Relieve symptoms, optimize growth (and bone density restoration), improve quality of life, minimize drug toxicity; mucosal healing (may change natural history of disease and decrease need for surgery)
 - b. Early treatment with biologics and immunomodulatory agents improves rates of mucosal healing and clinical remission.
 - c. Noninvasive biomarkers of mucosal healing (i.e., fecal calprotectin) useful to monitor resolution/recurrence of intestinal inflammation, but cutoff values unclear
 - d. Optimize disease-modifying agents (immunomodulators, biologics, surgical resection).

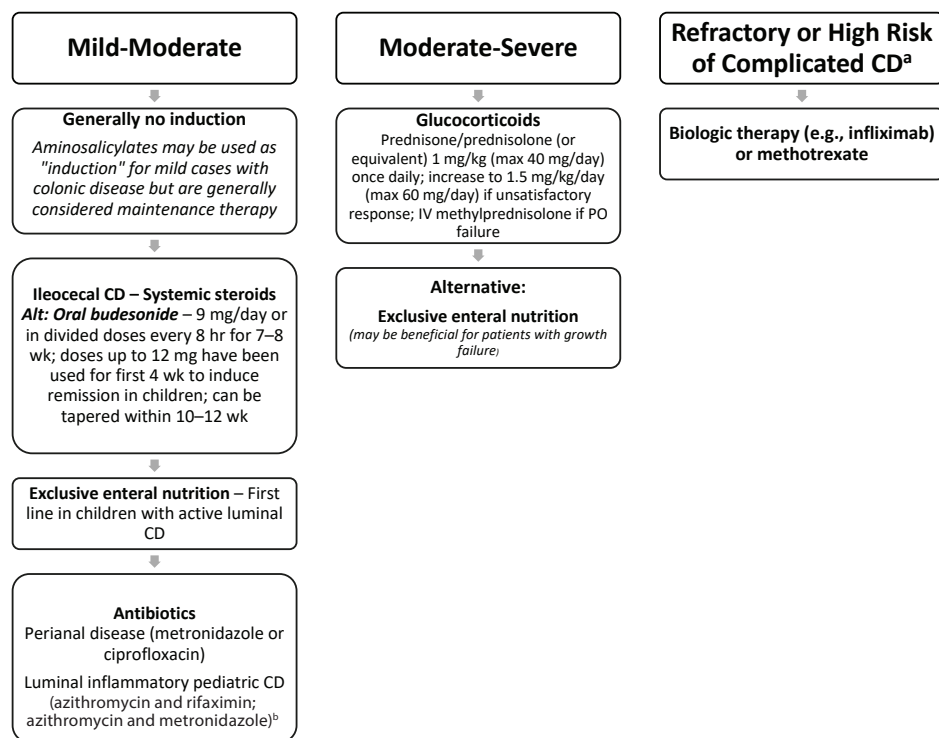
- e. Location of diseases important to medical management
 - i. Budesonide effective for ileum and ascending colon
 - ii. Aminosalicylate enemas effective for rectum and left colon
- f. Treatment includes both induction and maintenance phases. Available guidelines vary in treatment approach. The following is a review of general treatment strategies (available guidelines: ACG, NICE, AGA, ECCO-NASPGHAN).
- g. Disease severity important when selecting treatment approach – Based on Pediatric Crohn's Disease Activity Index (Table 11)
 - i. Scoring tool ranging from 0 to 100
 - ii. Factors based on child's well-being, degree of abdominal pain, BMs, weight gain, linear growth, physical examination, hematocrit, sedimentation rate, serum albumin

Table 11. Pediatric Crohn's Disease Activity Index for Severity Scoring^a

Score	Severity Rating
0–10	Inactive disease
11–30	Mild disease activity
> 30	Moderate to severe

^aA decrease in score of ≥ 12.5 reflects a clinical response and generally a decrease in severity rating (i.e., move from moderate/severe to mild). Information from: Hyams JS, Ferry GD, Mandel FS, et al. Development and validation of a pediatric Crohn's disease activity index. *J Pediatr Gastroenterol Nutr* 1991;12:439.

2. Induction of remission (Figure 1)

**Figure 1.** Initial (induction) Crohn disease treatment regimens according to severity.

CD = Crohn disease; IV = intravenous(ly); PO = oral(ly).

^aAt high risk of complications: Extensive small bowel disease/severe ulceration, growth failure in puberty, severe perianal disease, steroid-refractory disease.

^bAzithromycin and metronidazole combination therapy has been studied for induction but showed no difference between combination therapy and metronidazole alone and was not compared against standard therapy (Expert Rev Gastroenterology Hepatol 2021;15:891-908).

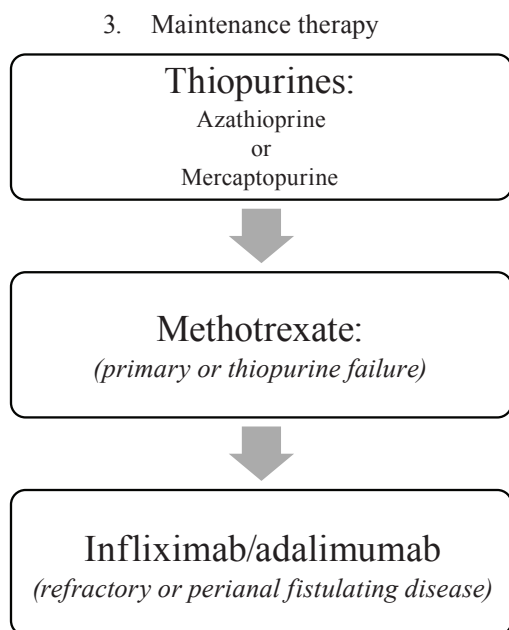


Figure 2. Maintenance Crohn disease treatment.

a. Main therapeutic agents (Table 12)

Table 12. Summary of Main Therapeutic Agents for Induction and Maintenance of CD

Agent/Strategy	Therapy Notes
Exclusive enteral nutrition (EEN) (according to European recommendations)	- Efficacy similar to steroids for induction (healing rates 19%–75%); however, newer data suggest EEN is associated with earlier remission and avoidance of steroids over the 6-yr study follow-up (J Crohns Colitis 2017;11:1063-70) - No significant differences in growth, hospitalization, or need for biologics or surgery were found - Consists of oral feeds with whole proteins; elemental formulas if specific medical indication - Formulas are typically administered via NG tube. No solid foods are introduced until weaning off EEN; some studies suggest an oral diet mimicking EEN may be as effective and better tolerated than EEN (Gastroenterology 2018;156:1354-67.e6) 6–8 wk duration followed by taper (gradual food reintroduction and decrease in formula volume every 2 or 3 days over 2–3 wk)
Corticosteroids	- Prednisone/prednisolone preferred; short term – Should see response in 1–2 wk - PO steroids preferred. If not tolerated, IV steroids (methylprednisolone) can be used “Steroid-dependent” considered high dose for > 2–3 mo, daily steroids for 4–6 mo, or frequent exacerbations during steroid tapers - Oral budesonide alternative - pH-dependent budesonide tablet (Uceris) and controlled ileal-release budesonide capsule (Entocort – FDA approved in April 2016 for mild to moderate active CD involving the ileum and/or the ascending colon in patients ≥ 8 yr weighing > 25 kg) - Adverse effects - Hypertension - Mood/behavior changes (insomnia) - Adrenal suppression (as early as 1 wk) - Growth retardation (use steroid-sparing strategies)

Table 12. Summary of Main Therapeutic Agents for Induction and Maintenance of CD (*continued*)

Agent/Strategy	Therapy Notes
Thiopurines Azathioprine Mercaptopurine	• Block purine synthesis; halt replication of DNA • May take 8–14 wk for maximum effect • TPMT activity testing (biochemical activity testing superior to genotype test) recommended before treatment: Identifies patients at risk of early profound myelosuppression ◦ Homozygous for mutation – No or low enzyme activity – Contraindicated ◦ Heterozygous for gene mutation/intermediate activity – Decrease dose by 50%–75% • Adverse effects ◦ Hematologic (leukopenia, thrombocytopenia) ◦ Infections ◦ Pancreatitis ◦ Flu-like/acute GI symptoms ◦ Increased transaminases ◦ Lymphoma (avoid thiopurines during Epstein-Barr virus because of risk of EBV lymphoma) • Can obtain thiopurine metabolite concentrations for monitoring efficacy and toxicity • Dermatologic screening (current and past users)
Methotrexate	• Irreversibly binds to and inhibits dihydrofolate reductase, thereby inhibiting purine synthesis and DNA synthesis • Contraindicated in pregnancy or within 3 mo of planned pregnancy (females and male partners) – Requires birth control methods • Maximum of 25 mg (15 mg/m²) intramuscular or subcutaneous (more effective than oral route) weekly • Oral folate supplement advised • Adverse effects ◦ Nausea/vomiting ◦ Flu-like symptoms, myelosuppression (rare) ◦ Pulmonary toxicity (rare, but serious) ◦ Teratogenic ◦ Elevated transaminases (up to 30% of patients)

Table 12. Summary of Main Therapeutic Agents for Induction and Maintenance of CD (*continued*)

Agent/Strategy	Therapy Notes
Biologic therapy (anti–tumor necrosis factor [TNF])	• Chimeric monoclonal antibody that binds to TNFα • Infliximab and adalimumab have similar efficacy and adverse event profiles. Long-term safety and efficacy similar to adults. Results of IMaGINE 2 study (extension of IMaGINE 1, a 52-wk safety and efficacy evaluation of adalimumab in pediatric patients with moderate to severe CD) found no new safety issues (Inflamm Bowel Dis 2017;23:453-60) ◦ Infliximab dosing (≥ 6 yr and adolescents): 5 mg/kg/dose at 0, 2, and 6 wk; followed by maintenance of 5 mg/kg/dose every 8 wk ◦ Adalimumab dosing (≥ 6 years and adolescents): 17 to <40 kg, SUBQ: 80 mg on day 1, then 40 mg administered 2 wk later; maintenance (beginning day 29): 20 mg every other week; ≥ 40 kg, SUBQ: 160 mg (day 1 or split over 2 days), then 80 mg 2 wk later; maintenance (beginning day 29) 40 mg every other week • Mandatory tuberculosis testing before therapy initiation and annually • Hepatitis B screening recommended before therapy • Consider screening for live vaccine immunization compliance because therapy initiation can be delayed for 4–6 wk after vaccination • Adverse effects ◦ Anti-TNF antibody formation: Infusion-related reactions and delayed hypersensitivity reactions (hypoxia or hypotension are contraindications to therapy) ▪ Premedications can be considered in those with a history of mild/moderate reactions; blanket preemptive premedication has been discouraged but is highly reported ▪ TDM, drug antibody evaluation, dose and/or frequency gradual increases, or concomitant therapy with an immunomodulator are strategies mentioned in overcoming/preventing immunogenicity (World J Gastrointest Pharmacol Ther 2017;8:155-61) ◦ Infection risk – including opportunistic infections ◦ Hepatosplenic T-cell lymphoma • <i>Note on biosimilars:</i> ◦ A biosimilar is a biologic product that is approved on the basis of showing that it is highly similar to an FDA-approved product with no major safety or effectiveness differences ◦ Infliximab-dyyb (Inflectra, Celltrion), infliximab-abda (Renflexis, Samsung Bioepis), infliximab-qbtx (Ixifi, Pfizer), infliximab-axxq (Avsola, Amgen) are also now approved and have been used in the adult population. Prospective, observational studies of pediatric patients with IBD have shown similar clinical results and lower costs (Arch Dis Child 2018;103:89-91; J Pediatr Gastroenterol Nutr 2017;65:285-8; J Crohns Colitis 2016;10:127-32) ◦ Adalimumab biosimilars adalimumab-atto (Amjevita, Amgen), adalimumab-adbm (Cyltezo, Boehringer Ingelheim), adalimumab-afzb (Abrilada, Pfizer), and adalimumab-fkjp (Hulio, Mylan) are available • Limited pediatric data on other biologics (the selective adhesion-molecule inhibitors vedolizumab and natalizumab). There are a few retrospective studies and case reports using the interleukin-12 and -23 inhibitor ustekinumab in patients that have failed TNF-modulator therapy.

SUBQ = subcutaneous; TDM = therapeutic drug monitoring; TPMT = thiopurine methyltransferase.

- b. Less common therapeutic agents
 - i. Natalizumab, vedolizumab, ustekinumab
 - (a) Natalizumab studied as an induction agent in adolescents and adults with moderate to severe CD showed clinical response and, to a lower degree, remission.
 - (1) Dosing of 3 mg/kg at 0, 4, and 8 weeks
 - (2) Prior safety concerns of cases of PML (progressive multifocal leukoencephalopathy) arose, leading to a retrospective safety evaluation before it returned to the market in 2007.
 - (3) A Cochrane review listed natalizumab as an option for induction, and the benefits of the drug should be weighed against the potential adverse effects.
 - (b) Vedolizumab was also studied as induction and maintenance therapy for CD in adults, showing an almost 8% increase in 6-week clinical remission rates compared with placebo (N Engl J Med 2013;369:711-21). Studies of children have shown similar and conflicting results (J Crohns Colitis 2017;11:1230-7; Inflamm Bowel Dis 2016;22:2121-6; Inflamm Bowel Dis 2016;22:2425-31).
 - (c) Ustekinumab has limited data in the pediatric population. In a case series of four pediatric patients with CD, all previously receiving corticosteroids, methotrexate, azathioprine/mercaptopurine, and both infliximab and adalimumab, treatment with ustekinumab showed clinical response in only two children.
 - (1) Children included in these studies generally weighed more than 40 kg and received adult dosing of 300 mg at 0, 2, and 6 weeks for induction and 300 mg at 8-week intervals – OR, in smaller patients, data analyses reported using 5–6 mg/kg/dose on the same schedule
 - (2) Down-regulation of intestinal inflammation by inhibiting intestinal T-lymphocyte migration into the tissue is restricted to the GI tract, resulting in a potential decrease in systemic immunosuppression versus other agents.
 - ii. Thalidomide – may suppress TNF α production; increases NK (natural killer) cells, interleukin-2, and interferon- γ
 - (a) Data are insufficient to recommend thalidomide.
 - (b) Teratogenicity and adverse effect profile restrict use.
 - (c) Contraception is mandatory during therapy.
 - (d) Enrollment in REMS required.
 - iii. Aminosalicylates – may modulate inflammatory mediators (i.e., leukotrienes), inhibit TNF α
 - (a) Only recommended in patients with very mild disease because data do not support these agents as remission treatment for induction or maintenance phases of therapy
 - (b) Sulfasalazine is superior to other aminosalicylates for induction in adults with colonic disease.
 - (c) Patients with Crohn ileitis who do not have colonic involvement should be treated with mesalamine because sulfasalazine is not designed for ileal release.
 - (d) Viewed as adjuvant therapy because not shown to provide mucosal healing. Verify mucosal healing if used as sole therapy.
 - (e) Sulfasalazine dosing
 - (1) Similar to that in pediatric UC
 - (2) Initiate gradually; may start at 30–40 mg/kg/day, depending on the patient's tolerance; up to 50–80 mg/kg/day orally (up to 4 g/day)
 - (3) Supplemental folic acid (1 mg/day) should be given to all patients taking sulfasalazine.
 - (f) Adverse effects and monitoring (see UC section for agent-specific information)
- 4. Step-down/exit therapy strategies
 - a. Immunosuppressives and anti-TNF agents should be continued for a prolonged period (years), if effective.

- b. After growth and puberty, can consider discontinuing therapy if patient has sustained steroid-free remission for several years, but first, verify complete mucosal healing
 - c. Step down from combination (anti-TNF agents plus methotrexate or thiopurines) to anti-TNF agents after 6 months with complete mucosal healing.
 - d. If step-down therapy from anti-TNF agent is chosen, should be to methotrexate or thiopurines
- E. Presentation/Clinical Findings of UC
1. Usually presents in teenage years, but can occur earlier
 2. Presentation is similar to adults and is usually characterized by diarrhea (often containing blood), anemia, weakness, abdominal pain, and sometimes weight loss. Severe presentation may also include severe abdominal pain, frank blood with diarrhea, tenesmus, fever, leukocytosis, and hypoalbuminemia.
 3. Disease is limited to the colon (unlike CD) – Ultimate “cure” is colectomy, but would result in permanent ileostomy or creation of ileoanal reservoir
- F. UC Treatment
1. Goals and principles
 - a. Although surgery would “cure,” goal of medical therapy is to control the disease and allow the patient to retain colon for as long as possible.
 - b. In general, same principles as in adult therapy, but greater concern with long-term steroid therapy (impact on overall growth)
 - c. Treatment is based on the severity.
 - i. Use the Pediatric Ulcerative Colitis Activity Index (Gastroenterology 2007;133:423) (Table 13).
 - ii. Scoring tool 0–85
 - iii. Based on abdominal pain, rectal bleeding, stool consistency, number of stools every 24 hours, nocturnal stools, activity level

Table 13. Pediatric UC Activity Index for Severity Scoring and Initial Treatment

Recommendations (scores 0–85)

Score	Severity	Physical Findings	Treatment
0–9	Remission	N/A	Maintenance/taper therapy
10–34	Mild disease	Disease extending beyond the rectum < 4 BMs a day Without significant abdominal pain, anemia, fever	Oral 5-ASA (mesalamine or sulfasalazine)
35–64	Moderate disease	> 4 bloody BMs per day Intermittent abdominal pain No tenesmus or fever	Oral corticosteroid Alternative: PO budesonide IV steroids may be used if unresponsive to PO steroids within 1–2 wk or with poor fluid intake
65–85	Severe disease	Profuse, bloody diarrhea Abdominal distension or tenderness Signs of systemic illness	Hospitalization and surgical consultation Evaluate for <i>C. difficile</i> High-dose IV corticosteroids (methylprednisolone) Oral 5-ASA preparations are discontinued during acute exacerbations (not effective)

5-ASA = aminosalicylate; N/A = not applicable.

Turner D, Otley AR, Mack D, et al. Development, validation, and evaluation of a Pediatric Ulcerative Colitis Activity Index: a prospective multicenter study. *Gastroenterology* 2007;133:423-32.

2. Proctitis
 - a. Disease limited to the rectum
 - b. May receive topical therapy for moderate inflammation
 - c. Topical hydrocortisone enema or foam
 - i. Enema – Colocort, Cortenema (100 mg/60 mL)
 - ii. Foam – Cortifoam (90 mg/applicator)
 - iii. Adolescents and adults – 1 application once or twice daily for 2–3 weeks
 - iv. Administration: Patients should lie on their left side during administration and for 30 minutes afterward; retain enema for at least 1 hour, preferably overnight. Antidiarrheal medication or sedation may be used to facilitate retention of enema.
 - d. Topical aminosalicylate (mesalamine) enema or suppository
 - i. Enema – Rowasa (4 g/60 mL)
 - ii. Suppository – Canasa 1000 mg
 - iii. Adolescents and adults – (enema) 4 g once daily at bedtime; (suppository) 500 mg once daily at bedtime (some have used twice daily)
 - e. Combination of oral and rectal may be used to induce remission if topical therapy alone is not effective.
3. Mild disease
 - a. First-line therapy: Oral aminosalicylate (usually mesalamine or sulfasalazine)
 - b. Moderately effective for mild disease and fewer adverse effects than corticosteroids
 - c. Mild disease may respond to rectal therapy alone, but better adherence with oral preparations
 - d. Most pediatric studies have used mesalamine or sulfasalazine, no head-to-head trials, so decision for therapy is based on adverse effects, cost, and availability
 - e. Mesalamine: 50–75 mg/kg/day divided two or three times daily (max 4.8 g/day)
 - i. Limited data on the efficacy/safety of extended-release products in children
 - ii. Available as delayed-release capsule, extended-release capsule, enema, suppository, and delayed-release tablet – See earlier route discussion.
 - iii. Advantages: Fewer adverse effects than sulfasalazine; capsules can be opened into water or acidic food (consume immediately)
 - f. Sulfasalazine: Has a unique mechanism of action – reduced in the colon by coliform bacterial enzyme (azoreductase) to aminosalicylate and sulfapyridine. Initial dose – 25 mg/kg/day divided two or three times daily, advance over 1 week to full dose of 50–75 mg/kg/day divided two or three times daily
 - i. Larger children and adults may use 1–2 g/day, titrated to 4–6 g/day, divided three or four times daily.
 - ii. Supplement with folic acid (1 mg/day).
 - iii. Advantages: May be compounded as liquid dosage form, lower cost
 - iv. Disadvantages: More adverse effects than mesalamine (headache, rashes). Higher risk of allergic response in those with sulfa allergy – AVOID
 - v. Adverse effects: Diarrhea, folate malabsorption (competes with folic acid for absorption, will need to supplement), headache, bone marrow suppression, rash, fever, hepatotoxicity
 - vi. Monitoring: CBC, liver function tests renal function tests, stool frequency, hematocrit, reticulocyte count
 - g. Balsalazide: 75–100 mg/kg per DOSE given three times daily
 - i. Adult studies suggest that it is more effective than mesalamine.
 - ii. May cause paradoxical watery diarrhea in the first few weeks of therapy
 - h. Olsalazine: Limited pediatric data: 30 mg/kg/day. May cause paradoxical watery diarrhea in the first few weeks of therapy

4. Moderate disease
 - a. Steroid-responsive patients usually have some improvement after 1 week of oral treatment.
 - b. First line: Oral prednisone – 1–1.5 mg/kg/day, up to a maximum of 40–60 mg/day
 - c. Alternative: Oral budesonide
 - i. Adult dose of 9 mg in the morning for 8 weeks
 - ii. Fewer adverse effects
 - iii. Meta-analysis showed budesonide no more effective than placebo (adult studies)
 - d. If patient is nonresponsive after 1–2 weeks, admit to hospital for intravenous corticosteroids.
 - i. Methylprednisolone 1 mg/kg/dose every 12 hours (max 60 mg/day)
 - ii. Bowel rest and intravenous fluids – Not shown to speed remission, but do help with symptom relief
 - e. Steroid-responsive disease
 - i. If improvement after 1 week of intravenous steroids, transition to oral steroids and mesalamine (or other aminosalicylate) and continue for 2–4 weeks; then taper during the next 2 months
 - ii. Dosing: Prednisone 1–2 mg/kg/day (max 40–60 mg/day)
 - f. Steroid-dependent disease
 - i. If high-dose steroid for more than 2–3 months or daily steroids for 4–6 months, or frequent exacerbation during steroid taper, immunomodulator or infliximab may be indicated
 - (a) Mercaptopurine or azathioprine
 - (1) Measure *TPMT* phenotype activity to see if at risk of toxicity (therapy contraindicated if homozygous for mutation)
 - (2) Dosing: Mercaptopurine at 1–1.5 mg/kg/day or azathioprine at 2–3 mg/kg/day
 - (3) Monitoring: Bone marrow suppression, hepatotoxicity (same as PCD)
 - (b) Infliximab – Loss of response over time
 - ii. Methotrexate has limited data in pediatric patients with UC.
5. Severe disease
 - a. Considered an emergency, and patient should be admitted to the hospital with surgical consultation
 - b. Electrolyte/fluid management
 - c. Replacement of blood and/or albumin
 - d. Evaluate for *C. difficile* infection and toxic megacolon.
 - e. Antibiotic therapy has not been supported by evidence (may give broad-spectrum antibiotics until cultures return negative).
 - f. Nutrition management
 - i. If can tolerate oral administration, continue regular diet
 - ii. PN may be required until clinical improvement.
 - iii. Watch for hypokalemia or opioid use, which may trigger toxic megacolon.
 - g. Medical therapy
 - i. High-dose steroids: Methylprednisolone – 1 mg/kg/dose every 12 hours (max 30 mg every 12 hours)
 - ii. Discontinue oral aminosalicylate (ineffective in acute severe exacerbations of colitis).
6. Pain management
 - a. No consensus. May use acetaminophen, but watch for escalating symptoms and do not want to mask infectious signs/symptoms
 - b. Avoid opioids because of the risk of toxic megacolon – Low-dose morphine (0.05 mg/kg/dose) and extended interval may be used occasionally for refractory cases.
 - c. Avoid NSAID use – Associated with exacerbation of disease
 - d. Anxiolytic therapy may be helpful.

7. Maintenance
 - a. Aminosalicylate is preferred once the disease is in remission.
 - b. If patient is intolerant of agent or does not stay in remission, may try mercaptopurine or azathioprine
8. Refractory disease therapy options
 - a. Colectomy for uncontrolled hemorrhage, complications (toxic megacolon or bowel perforation, or patients with no improvement after 7- to 10-day course of high-dose steroid treatment)
 - b. If patient does not wish to undergo surgery, salvage medication therapy can be tried. Data with these medications show that the remission rate is at least 75% but that most patients still go on to have a colectomy.
 - c. Infliximab: Use in UC is less supported than in PCD, but some small pediatric case series and one multicenter study of 60 patients showed a 73%–75% initial response rate and a long-term rate (1 year) of around 54%–64%.
 - d. Tofacitinib: Orally administered JAK1 and JAK3 tyrosine kinase inhibitor used in juvenile idiopathic arthritis. (Note: Oral solution and extended-release tablets are not bioequivalent and cannot be substituted on a mg:mg basis). Has been used in adult patients as an alternative agent in refractory patients. In an FDA safety review released in 2021, an increased risk of cardiovascular-related events, cancer, thrombosis, and death were reported, and boxed warnings were added. Use was limited to patients who have not responded to or cannot tolerate one or more TNF-blockers.
 - e. Intravenous cyclosporine
 - i. Dose: 2–4 mg/kg/day
 - ii. Has been shown to induce remission in adult patients, allowing them to avoid a colectomy
 - iii. Oral microemulsion cyclosporine may also be effective, but few reports in children
 - iv. Monitoring: Serum concentrations 12 hours after dose or immediately before next dose may be obtained; general reference range 100–400 ng/mL; studies report targets of 150–250 ng/mL on 2 mg/kg/day and 300–350 ng/mL for 4 mg/kg/day
 - f. Tacrolimus
 - i. Dose: 0.1 mg/kg per dose given twice daily
 - ii. Efficacy similar to intravenous cyclosporine
 - iii. Monitoring: Serum trough concentrations reported in studies range from 5 to 10 ng/mL and are up to 10–15 ng/mL, with the higher trough used for initial therapy, then lower trough, but optimal trough concentrations have not been determined
 - iv. Rectal tacrolimus enemas have been used for IBD-related proctitis not responding to conventional therapies in adult patients. A case report in an 8-year-old girl used rectal tacrolimus at 2 mg/day in the evening for 4 weeks with improved response. Therapy was reduced to 2 mg/week with no relapses. No adverse effects were noted in the case report (Clin J Gastroenterol 2014;7:320-323)
 - g. If used, cyclosporine and tacrolimus should either be transitioned to mercaptopurine or the patient should undergo surgery within 6 months – Disadvantages include infection, nephrotoxicity, and neurotoxicity for calcineurin inhibitor.
 - h. Sequential therapy has been used in adults.
 - i. Infliximab followed by cyclosporine or tacrolimus, or vice versa
 - ii. Not recommended because of high rate of serious infections and mortality – Progression to surgery is recommended over sequential therapy.

Patient Cases

7. A 15-year-old male adolescent received a diagnosis of CD of the colon 6 months ago. He has had active disease, despite 5 months of mercaptopurine therapy and two courses of corticosteroid therapy. Which is most likely to induce remission?
 - A. Azathioprine.
 - B. Infliximab.
 - C. Mesalamine.
 - D. Methotrexate.
8. A 17-year-old female adolescent presents with an 8-week history of new-onset abdominal pain and 3 or 4 bloody stools per day. She reports an allergy to “sulfa”-containing medications (documented as wheezing). Colonoscopy reveals UC, with lesions extending beyond the rectum. Which is best for this patient?
 - A. Rectal mesalamine.
 - B. Oral mesalamine.
 - C. Oral sulfasalazine.
 - D. Intravenous methylprednisolone.

VI. SHORT BOWEL SYNDROME**A. Definition**

1. Most common cause of intestinal failure
2. *Intestinal failure* refers to the inability of the GI tract to maintain adequate hydration and nutrient balance without using intravenous or enteral supplementation. American Society for Parenteral and Enteral Nutrition defines it as dependence on supplemental parenteral support for a minimum of 60 days within a 74 consecutive day interval (J Parenter Enteral Nutr 2022;46:42-59).
3. Can be considered anatomic or functional loss of more than 50% of the normal small intestine leading to malabsorption of macro- and micronutrients

B. Epidemiology/Etiology

1. Incidence ranges from 2 to 6.8 per 1 million population.
2. Surgical SBS occurs in 7 of 1000 live births in neonates weighing less than 1500 g.
3. Increased risk is inversely proportional to birth weight and gestational age.
4. Can result from:
 - a. Massive resection of small intestine – Degree of resection required to cause malabsorption will vary between individuals and may depend on age at time of initial resection.
 - b. Abnormal gut motility
 - c. Mucosal disorders that disrupt absorption or digestion
 - d. Congenital intestinal anomaly that may affect or lead to any of the above causes, including (often resulting in bowel resection):
 - i. Intestinal atresias – May occur in any area along the small intestine and can be continuous or segmented; obstruction may lead to ischemia, necrotic bowel, and gut resection
 - ii. Gastroschisis – Caused by an abdominal wall defect leading to bowel ischemia and need for gut resection
 - iii. Necrotizing enterocolitis – Especially common in preterm neonates (see neonatal chapter)

- e. Older infants and children – Leading to resection
 - i. Malrotation with volvulus – Occlusion of the mesenteric artery leading to ischemia
 - ii. Hernias and intussusception are common causes in older infants and children
 - f. Older children and adults – Leading to resection
 - i. CD
 - ii. Abdominal tumors
 - iii. Radiation enteritis
- C. Pathogenesis
1. SBS is characterized by diarrhea, malabsorption, fluid and electrolyte imbalances, and, ultimately, malnutrition.
 - a. Children are susceptible to complications, even if only small amount of bowel resection or early in infancy.
 2. For surgical resection of both affected gut and nonfunctional bowel, the length and “type” of remaining functional bowel (small intestine vs. colon) determine the potential for chronic complications in SBS and ability to resume an oral diet.
 - a. Goal is to meet nutrition and growth needs on enteral nutrition.
 - b. Most patients will be discharged on both enteral nutrition and PN and are transitioned to enteral nutrition only as the gut adapts.
 3. Influence of the length of remaining bowel
 - a. Difficult to predict how much this affects ability to feed enterally
 - b. Example: Term neonate
 - i. Length of the intestine is 240 cm, colon is 40 cm
 - ii. Goal can be achieved with as little as 15 cm of jejunum and ileum IF ileocecal valve is intact or 40 cm if no ileocecal valve; assumes normal function of remaining bowel
 4. Remaining segments of intestine and intestinal motility
 - a. Important for determining metabolic consequences
 - b. Proximal small intestine – Duodenum and jejunum
 - i. Absorption of proteins, carbohydrates, and fats
 - ii. Water-soluble nutrients absorbed in jejunum
 - iii. Minerals
 - iv. Ileum can compensate for loss of proximal small intestine through adaptation.
 - c. Ileum
 - i. Only site for vitamin B₁₂ and bile salt absorption
 - (a) Malabsorption of bile salts leads to increased production by the liver, but losses can exceed production.
 - (b) Low bile can cause further malabsorption of fat and fat-soluble vitamins.
 - (c) Can cause bilious diarrhea (also by ileal resection)
 - (d) Increased risk of renal oxalate stones
 - ii. Unabsorbed lipids in ileum cause a delay in gastric emptying, which may help in absorbing other nutrients in the small intestine.
 - iii. Motility issues because ileum is also site of GI hormone production (enteroglucagon and peptide YY)
 - d. Ileocecal valve
 - i. Presence or absence of ileocecal valve does not affect mortality but does affect length of time on PN.
 - ii. Loss of valve reduces small intestine transit time, which impairs nutrient absorption and greatly increases diarrhea.

- iii. Valve also serves as a barrier to the translocation of colonic bacteria into the terminal ileum.
 - (a) Bacterial translocation associated with malabsorption of fats, vitamin B₁₂, and bile salts
 - (b) Causes increased D-lactic acid exposure through inability to metabolize and lack of absorption in small bowel and more colonic exposure, leading to ataxia, dysarthria, and confusion
 - e. Colon
 - i. Plays an important role in water and electrolyte absorption
 - ii. Usually requires long-term PN (or intravenous hydration) if large resections
 - iii. Colonic preservation leads to water and electrolyte homeostasis as well as energy balance. Bacterial carbohydrate fermentation in colon leads to production of short-chain fatty acids, which can provide additional calories.
 - 5. Intestinal adaptation
 - a. Occurs when intestinal continuity is preserved (why primary anastomosis is ideal) and with earlier enteral nutrition initiation
 - b. Begins within 48 hours of resection and may continue for up to 3 years
 - c. Absence of ostomy increases water and electrolyte absorption and may result in stimulation of the colon to have a more adaptive function.
 - d. The ileum can adapt to take on the functions of the jejunum, whereas the jejunum has a decreased capacity to adapt to ileal functionality.
 - e. Several mechanisms of adaptation
 - i. Lengthening of intestinal villi – Leads to increase in absorptive capacity
 - ii. Small bowel dilation – Leads to increased absorptive surface area
 - iii. Exposure of the remaining enterocytes to luminal nutrients leads to absorptive changes by enterocyte-derived mediators like glucagon-like peptide 2.
 - 6. Common morbidities include:
 - a. Sepsis (central line and bacterial overgrowth related)
 - b. PN cholestasis
 - c. 10%–15% of patients have neurologic and development defects
 - 7. Controversy with management in small infants with only 20–40 cm of bowel remaining with respect to intestinal transplantation
- D. Nutrition Management
- 1. Phase I: Early initiation of PN and prevention of electrolyte abnormalities (see Fluids, Electrolytes, and Nutrition chapter)
 - a. Duration of PN depends on:
 - i. Length and site of remaining bowel
 - ii. Presence of bacterial overgrowth
 - iii. Degree of hepatobiliary disease (cholestasis)
 - iv. Ability to maintain adequate hydration
 - v. Tolerance of enteral nutrition
 - vi. Quality of growth
 - b. Watch for gastric hypersecretion, which can deactivate pancreatic enzymes and reduce optimal pH for fat absorption and promote bacterial overgrowth.
 - i. Give H₂RA or PPI – Will help with fluid and nutrient absorption
 - ii. Useful in early phase after resection
 - iii. Should resolve after first few months of surgery, and therapy may be indicated for 6 months or more after initial resection

2. Phase 2: Early initiation of enteral feeds, if possible
 - a. Helps reduce diarrhea and improve intestinal adaptation
 - b. Start once the patient has achieved growth on PN and the patient's fluid/electrolytes are stable.
 - c. Continuous feeding schedule
 - i. Better tolerated
 - ii. Allows more total nutrient absorption
 - iii. Emesis, abdominal distension, and increased ostomy output are decreased with gradual increases in continuous feeding rate.
 - d. Wean PN gradually. Can transition to cyclic schedule – Increasing time off PN by 2–4 hours until PN given over 8–12 hours (overnight infusion)
 - e. Success in this phase is predicted by how well the enteral nutrition is tolerated as well as ostomy output and overall growth.
 - f. Indicators for halting feeding advancement
 - i. Vomiting or increase in stool output by more than 50% (or greater than 40–50 mL/kg)
 - ii. Positive stool-reducing substances
 - iii. Significant skin breakdown in diaper area
 - g. Optimal enteral nutrition formula
 - i. Elemental, semi-elemental, peptide-based formulas have historically been used and have similar caloric absorption in adult patients.
 - (a) Most studies show no difference in growth between hydrolyzed and non-hydrolyzed formulas.
 - (b) Site and amount of remaining intestine may allow for use of “normal” formulas.
 - ii. Breast milk
 - (a) Can be used, even though not hydrolyzed
 - (b) Contains immunoglobulins and growth factors, which may improve intestinal adaptation
 - iii. Protein hydrolysate– or amino acid–containing formulas are primarily used in infants and children because:
 - (a) Allergic response more common in children with disrupted mucosal barrier
 - (b) Protein hydrolysate considered standard of care, but can use amino acid–based formula if intolerance to protein hydrolysate
 - (c) Examples: Pregestimil, Alimentum (semi-elemental); Neocate (elemental for neonates); Peptamen Junior (semi-elemental for children older than 1 year)
 - iv. Medium-chain triglycerides versus long-chain fatty acids
 - (a) Medium-chain triglycerides are more water soluble and better absorbed but have a higher osmotic effect and do not provide essential fatty acids.
 - (b) Preferred use of long-chain fatty acids
 - v. Excess carbohydrate content
 - (a) Osmotic effects, leading to diarrhea
 - (b) No more than 40% of total calories should be from carbohydrates. Some institutions may also dictate type of carbohydrates versus the amount.
 - h. Fluid, electrolyte, vitamin/mineral considerations
 - i. Increased sodium requirements if increased ostomy output or diarrhea (may require 4–8 mEq/kg/day)
 - ii. Sodium bicarbonate supplementation if metabolic acidosis from bacterial overgrowth
 - iii. Fat-soluble vitamins – A, D, E, K
 - (a) Use pediatric multivitamin preparation; water-soluble preparation preferred (e.g., DEKAs)
 - (b) Monitor concentrations at least yearly to check for toxicity.
 - (c) Vitamin K deficiency is rare unless patient is receiving broad-spectrum antibiotics.
 - iv. Vitamin B₁₂ injections may be necessary, especially in those with terminal ileum absence or partial resection.

- i. Fiber
 - i. Older infants and children with intact colon
 - ii. Soy polysaccharide and pectin
 - iii. Helps increase transit time, which increases absorption (increased contact time)
 - iv. Fiber that is not digested can be metabolized to short-chain fatty acids by bacteria, which provides energy to colonocytes.
 - v. Soluble fibers (pectin or guar gum) can be added to formula (initial dosing 1 g fiber per 100 mL); for patients with intact colon and no history or risk of bacterial overgrowth
 - j. Glutamine
 - i. In prematurity, glutamine is considered essential. With catabolic illness, glutamine may become essential
 - ii. Important energy source for mucosal cells
 - iii. Positive effects on intestinal adaptation in adults, but mixed results in pediatric patients
 - k. Growth hormone
 - i. Pediatric case reports suggest some benefit if the patient has low or decreased growth hormone responsiveness (e.g., somatropin; but no placebo-controlled trials).
 - ii. Wide variance among patient populations
 - iii. Most reports are with growth hormone and glutamine combination.
 - iv. No consensus for widespread use
 - l. Glucagon-like peptide 2
 - i. Enteroendocrine peptide released when intestinal lumen exposed to nutrients
 - ii. Used to start and enhance small bowel adaptive response
 - iii. Teduglutide (glucagon-like peptide 2 analog) (Gattex) has modest benefits in the treatment of adult SBS (has FDA approval for adult patients with SBS). In 2019, the FDA approved teduglutide down to 1 year of age for SBS. In one 12-week, open-label, multicenter trial of teduglutide in children, doses of 0.025 and 0.05 mg/kg/day were associated with reduced PN requirements and advancement of enteral feeding. All patients in the pooled dose cohorts (n=37) had at least one adverse effect, but all adverse effects were considered mild or moderate (J Pediatr 2017;181:102-111.e5). In the approval studies (24-weeks), children showed reduced volume of parenteral support and some with complete discontinuation of parenteral therapy.
3. Phase 3: Complete bowel adaptation
- a. Enteral nutrition is well tolerated, and oral feeds can be initiated.
 - b. Time interval – A few months to more than 1 year
 - i. Influenced by growth outcomes and presence/absence of metabolic complications
 - ii. Solid foods can be introduced at 4–6 months of age, or when developmentally appropriate (may be delayed if developmental delay or aversive feeding behaviors).
 - c. Small, more frequent meals may be needed.
 - i. Limit high-carbohydrate foods.
 - ii. Aim for high-protein, low- to moderate-fat foods.
 - d. May combine enteral nutrition with solid foods
- E. Complication Management
- 1. Infectious
 - a. Central venous line catheter infection: *Staphylococcus* spp. most common
 - b. Intestinal bacterial overgrowth
 - i. May migrate to bloodstream across gut wall
 - ii. Increased risk with:
 - (a) Cholestasis
 - (b) Acid suppression

- (c) Dysmotility
 - (d) Absence of ileocecal valve
- c. Management strategies (https://naspghan.org/wp-content/uploads/2021/03/Management_of_Central_Venous_Access_in_Children.26.pdf)
 - i. Chlorhexidine skin preparation
 - ii. Heparin and antibiotic-impregnated central venous catheters
 - iii. Ethanol and antibiotic lock therapy
 - (a) Ethanol and heparin are incompatible; if heparin is in PN or if heparin flushes are used for line care, ensure flushing with saline before and after lock to prevent contact.
 - (b) Ethanol therapy has also been implicated in increased central line catheter breakage (Pediatr Surg Int 2018;34:71-4) and may not be compatible with certain catheter types.
- 2. Thrombosis
 - a. Large vessel – Associated with central venous line catheters
 - b. Common in patients younger than 1 year (smaller vessel size)
 - c. May also be more common with dextrose concentrations greater than 25% in PN
 - d. Recurrent thrombosis may lead to superior vena cava syndrome and line access difficulties.
- 3. Cholestasis/PN-associated liver disease
 - a. Defined as conjugated bilirubin greater than 2 mg/dL in the absence of other causes of liver disease
 - b. See Fluids, Electrolytes, and Nutrition chapter.
- 4. Intestinal dysmotility (Table 14)
 - a. Constipation
 - i. Initially, the child with SBS may have diarrhea, but long term, constipation may be an issue because nerve signals can be disrupted after several resections, and strictures/adhesions are possible.
 - ii. Patients at increased risk of constipation:
 - (a) Cerebral palsy
 - (b) Inability to receive bolus feeds
 - (c) Prolonged use of refined enteral formulas
 - (d) Inadequate fluid balance
 - b. Diarrhea
 - i. Treatment threshold lower than with diarrhea from other causes secondary to long-term nutrition needs
 - ii. Cholestyramine – For diarrhea associated with bile salt malabsorption (resection of terminal ileum); not for use in patients with bile acid deficiency
 - iii. Loperamide – For chronic diarrhea in older infants and children
 - (a) May cause bacterial overgrowth and worsen malabsorption; would avoid in these patients
 - (b) Tablet may be preferred because of the high sugar content of the liquid formulation.
 - iv. Diphenoxylate and atropine
 - (a) Opioid agonist used to decrease GI motility, atropine used to discourage abuse
 - (b) Limited data on routine and prolonged use in pediatric patients
 - v. Octreotide – Effects are dose-dependent; increases small bowel transit time occur with lower doses, while higher doses slow intestinal motility
 - (a) Tachyphylaxis develops over time
 - (b) May prevent adaptation
 - (c) Increases risk of gallstone development and glucose dysregulation (hyperglycemia [common] and hypoglycemia [occurs in adults with brittle diabetes mellitus])
 - (d) Generally reserved for later in therapy (2 years or more after SBS diagnosis and after adaptation period)

5. Vitamin and mineral deficiencies (depending on site and extent of resection)
 - a. Iron deficiency
 - b. B₁₂
 - c. Folic acid
 - d. Copper
 - e. Fat-soluble vitamins

Table 14. Select Medications Used to Manage SBS Motility Complications (Diarrhea)

Medication	Mechanism	Products Available	Notes
Cholestyramine	Forms a nonabsorbable complex with bile acids in the intestine, inhibits reuptake of intestinal bile salts	4-g packets	For diarrhea associated with increased bile acids Limited data on use; mix powder with 2–8 oz of water, noncarbonated liquid, or applesauce; do not hold in mouth for prolonged period Administer other drugs (including vitamins/minerals) at least 1 hr before or 4–6 hr after cholestyramine
Loperamide	Acts directly on intestinal muscles to inhibit peristalsis and prolong transit time	Liquid (1 mg/5 mL, 1 mg/7.5 mL) Tablet (2 mg)	Increase fluid intake to prevent dehydration Liquid formulation can increase diarrhea because of sugar content; tablets preferred Administration with high-fat meals can increase concentrations
Diphenoxylate and atropine (Lomotil)	Opioid agonist that inhibits GI motility and propulsion (atropine used to discourage abuse)	Solution (diphenoxylate 2.5 mg and atropine 0.025 mg per 5 mL)** **Only product approved for children younger than 13. Tablet (diphenoxylate 2.5 mg and atropine 0.025 mg)	Reduce dose as soon as symptoms are controlled; maintenance doses may be as low as 25% of initial dose If no improvement in 48 hr, medication is not likely to be effective Give before feeds/food for best effect Use with caution in inpatients with hepatorenal disease, renal dysfunction, acute UC, dehydration, cirrhosis
Octreotide	Synthetic polypeptide that mimics natural somatostatin by inhibiting serotonin release and secretion of motilin (also gastrin, vasoactive intestinal peptide [VIP], insulin, glucagon, secretin); inhibits growth hormone; decreases GI motility and inhibits intestinal secretion of water and electrolytes	Injection (Sandostatin): 50, 200, 500, and 1000 mcg/mL Intramuscular kit (depot) 10, 20, 30 mg	Continuous infusion generally used for diarrhea secondary to graft-vs.-host disease Low doses can increase GI motility; high doses decrease GI motility Intermittent dosing should begin with low range; titrate to response Monitor for: cholelithiasis, glucose control, thyroid function, fluid/electrolyte balance Used in only a few reports of children with SBS Caution should be exercised if using in intestinal transplant recipients because blood flow/supply to the graft could be altered as doses are increased

SC = subcutaneously.

Information from: Taketomo CK, Hodding JH, Kraus DM. Pediatric & Neonatal Dosage Handbook, 20th ed. Hudson, OH: Lexi-Comp, 2013.

F. Surgical Management

1. Indicated for patients who cannot wean from PN
2. Procedures are designed to lengthen intestines, thus increasing absorptive area.
 - a. LILT (longitudinal intestinal lengthening and tailoring) procedure (also known as Bianchi procedure)
 - b. STEP (serial transverse enteroplasty) procedure
 - c. Small bowel transplantation: Isolated intestinal transplantation indicated for patients with SBS with one of the following:
 - i. PN-induced liver disease
 - ii. Central venous catheter–related thrombosis of two or more central veins
 - iii. Frequent episodes of central line sepsis
 - iv. Frequent episodes of severe dehydration or major electrolyte issues despite PN and fluid administration
 - v. Intestinal failure with an intolerance of PN (e.g., frequent hospitalizations) or inability to function (e.g., high-output stoma)
 - vi. Underlying disease with increased risk of morbidity (e.g., residual bowel less than 10 cm in infants and less than 40 cm in older children)
3. Combined liver and small bowel transplantation
 - a. Indicated for patients with SBS AND if patient has irreversible PN-associated liver disease
 - i. Patient is considered likely to die within the next 2 years without transplantation
 - b. General lack of donors, but 5-year survival rate at experienced centers is 75%–78%
 - c. Deaths or graft losses generally occur with the first 30 months after transplantation, and most occur because of:
 - i. Technical failure
 - ii. Rejection
 - iii. Infection

Patient Case

9. A 32-day-old infant with SBS secondary to surgical necrotizing enterocolitis has been initiated on PN for fluid and electrolyte management postoperatively. The patient has an ostomy and has had 40 cm of small bowel removed. Which is the best strategy for supplying adequate fluid and nutrition to an infant with a postsurgical SBS?
 - A. Central access should be avoided because of the risk of line infections.
 - B. H₂RAs should be avoided in this population until complete bowel adaptation occurs.
 - C. Sodium replacement should be increased to account for ostomy losses.
 - D. Early introduction of antimotility agents should be considered.

VII. APPENDICITIS

A. Pathophysiology

1. Appendicitis occurs when there is an obstruction of the appendiceal lumen, causing pain and dilation and thickening of the lumen. Obstruction may be caused by:
 - a. Fecal material, undigested food, foreign material
 - b. Enlarged lymphoid follicle in the epithelial lining
 - c. Twisted or bent appendix

2. Once obstructed, bacterial overgrowth may occur after obstruction and breakdown of mucosal barrier, allowing the bacteria to invade the wall, causing inflammation, ischemia, gangrene, and eventually perforation. Bacteria involved: fecal flora, aerobic and anaerobic gram-negative rods (*E. coli*, *Peptostreptococcus* spp., *Bacteroides fragilis*, and *Pseudomonas* spp.)
3. Perforation is more likely after 72 hours of symptoms (but can occur after the first 12 hours) and will lead to peritonitis if the infection is not contained by the bowel loops and omentum.
4. Pathogens may cause infection of the appendix directly or cause swollen lymph nodes in the area, leading to appendicitis. Common pathogens are:
 - a. Adenovirus (cause of lymphoid hyperplasia associated with intussusception)
 - b. Rubeola virus (measles)
 - c. EBV
 - d. *Actinomyces israeli*
 - e. *Enterobius vermicularis* (pinworms)
 - f. *Ascaris lumbricoides* (roundworms)
5. Other potential causes may occur in the presence of other disease states, including CD, Burkitt lymphoma, cystic fibrosis, duplicate appendix, or appendiceal carcinoid tumor.
6. Differences in incidence and presentation from adults may occur because:
 - a. The appendix is funnel-shaped in the first year of life, making it less likely to become obstructed.
 - b. Peak incidence usually occurs in the adolescence, probably because of the presence of age-related enlargement of lymphoid follicles that line the appendix, causing obstruction.
 - c. Young children typically have more diffuse peritonitis, perhaps partly because of an underdeveloped omentum.

B. Epidemiology/Etiology

1. Appendicitis is the most common indication for pediatric emergency abdominal surgery.
2. Older children and adolescents are more likely to develop appendicitis than are younger children, but in young children, diagnosis is difficult because of nonspecific symptoms and the inability to accurately describe symptoms
 - a. incidence of 19–28 per 10,000 children younger than 14 years vs. 1–6 per 10,000 in children 0–4 years.
3. Because of the difficulty of diagnosing appendicitis in young children, the incidence of perforation is higher in young children, calling for special and timely attention to these patients in the presence of abdominal pain or other clinical symptoms (Table 15).

Table 15. Percentage of Perforation in Appendicitis Cases by Age Group

Age Group	Percentage (%)
Neonates	83
Children < 5 yr	51–84
5–12 yr	11–32
> 12 yr	10–20

C. Diagnosis

1. The Infectious Diseases Society of America (IDSA) guidelines recommend that all institutions have a clinical pathway for the diagnosis, treatment, discharge, and follow-up of appendicitis.
2. Pathway should include the characteristic constellation of findings, including abdominal pain, abdominal tenderness, and signs of acute inflammation (laboratory evidence), which will identify most cases (Table 16).

3. Laboratory findings
 - a. White blood cell count (WBC) or absolute neutrophil count is elevated in 96% of children with appendicitis (but also nonspecific).
 - b. C-reactive protein (CRP) may be elevated, but it is less sensitive for patients with symptoms for less than 24 hours. In the presence of perforation, CRP is more specific and may assist in making the diagnosis.
 - c. Procalcitonin is NOT routinely used in making the diagnosis because the WBC and CRP better identify patients with appendicitis than procalcitonin. Procalcitonin is also not elevated in patients with perforation.
4. Imaging – Completed according to the risk of appendicitis (may use the Pediatric Appendicitis Scoring Tool, refined low-risk appendicitis score; however, the MANTRELS (also known as Alvarado score) scoring tool is generally used in adults)
 - a. Helical computed tomography (CT) of abdomen and pelvis with intravenous contrast (NOT oral or rectal) is the recommended procedure for patients with suspected appendicitis.
 - b. Imaging should be done in all children (especially in those younger than 3 years when appendicitis diagnosis is not certain).
 - c. CT imaging is preferred, but ultrasonography is a reasonable alternative if avoiding the use of ionizing radiation in children
 - d. If imaging is negative, follow up at 24 hours to confirm resolution of signs and symptoms (low false-negative risk with imaging).

Table 16. Most Common Clinical Signs/Symptoms of Appendicitis By Age Group

Neonates (rare)	< 5 Yr (uncommon)	5–12 Yr	Adolescents/Adults
Abdominal distension Vomiting Decreased feeding Temperature instability Sepsis Lethargy Irritability	Abdominal pain Fever Vomiting Anorexia Rebound tenderness Guarding Abdominal distension Diarrhea (can be misdiagnosed as gastroenteritis)	Anorexia Vomiting Fever Diarrhea Nausea Right lower-quadrant abdominal tenderness Inability to walk Pain with percussion, hopping, or coughing	Anorexia Periumbilical pain (early) Right lower-quadrant pain and tenderness (develops about 24 hr after onset of symptoms) Vomiting Fever (24–48 hr after symptoms start) Guarding with abdominal palpation Positive Rovsing sign (palpation of the left lower quadrant of abdomen increases the pain felt in the right lower quadrant) ^a Pain on flexion and internal rotation of right hip or extension of the right hip ^a Rebound tenderness ^a

^aAlthough these signs are more difficult to use in children 3–12 years of age, there is a high specificity for acute appendicitis if they are present.

D. Treatment

1. Because of the more recent advances in the following practices, patient survival has approached 100%. The incidence of long-term sequelae has continued to decrease.

2. Antimicrobial therapy – Should be administered to all patients with a diagnosis of appendicitis (Table 17)
 - a. Appropriate therapy should include IDSA guideline–recommended agents that are effective against facultative and aerobic gram-negative organisms and anaerobic organisms found with community-acquired intra-abdominal infection.
 - b. Combination therapy
 - i. Advanced-generation cephalosporin plus metronidazole (preferred)
 - (a) Ceftriaxone (preferred)
 - (b) Ceftazidime
 - (c) Cefepime
 - ii. Combination of ceftriaxone and metronidazole is as effective as ampicillin/gentamicin/clindamycin in preventing abscess or wound infection, but antibiotic costs are lower.
 - iii. Clindamycin should be avoided because of increasing resistance.
 - iv. Aminoglycoside plus metronidazole
 - c. Single therapy
 - i. Carbapenem (meropenem, imipenem/cilastatin, ertapenem)
 - ii. β -Lactam/ β -lactamase inhibitor combination (piperacillin/tazobactam, ticarcillin/clavulanate)
 - iii. As effective as combination therapy in preventing complications of perforated appendicitis.
 - (a) Narrower-spectrum regimens less costly
 - (b) Extended-spectrum antibiotics associated with increased readmissions because of complications (Pediatrics 2016;138:e20154547)
 - (c) No difference in 30-day surgical site infection rates or hospital readmission rates (Ann Surg 2017 June 26 [Epub ahead of print])
 - d. Therapy duration
 - i. At least 5 days of intravenous antibiotics is recommended by the American Pediatric Surgical Association; however, shorter durations (3–5 days) have been reported with positive outcomes.
 - ii. If patients are still febrile at days 7–10, they should undergo imaging to check for an abdominal or pelvic abscess.

Table 17. Suggested Antibiotic Therapy for Appendicitis

Acute, nonperforated appendicitis	Ceftriaxone + metronidazole	24 hr around surgery (doses pre- and postoperative)
Perforated appendicitis	Ceftriaxone + metronidazole	Up to 14 days (assess at 5–7 days)

3. Operative intervention – Indicated for both acute, nonperforated appendicitis and perforated appendicitis. Treat with antimicrobial therapy, and maintain close inpatient follow-up.
4. Pain management/antipyretics – Postoperative pain
5. Intestinal motility issues
 - a. Can have paralytic ileus or intestinal obstruction from adhesions
 - b. Use nasogastric suction for patients with vomiting or abdominal distension postoperatively.
 - c. Oral fluids should be held until peritoneal inflammation and infection have improved (and/or ileus is resolved).
 - d. Advance diet slowly as tolerated.
6. Nutrition
 - a. PN would be warranted for a well-nourished child expected to be NPO (nothing by mouth) for more than 7 days or for 3–5 days in younger patients.
 - b. If the child is malnourished, begin PN within 48–72 hours after surgery.

Patient Case

10. A 16-year-old, previously healthy patient presents with nausea and periumbilical pain that has radiated to right lower-quadrant pain during the past 24 hours. She has been unable to eat since the symptoms began. Her temperature is 38.1°C (100.6°F), and physical examination reveals positive rebound tenderness. When asked to cough, she winces in pain. Her CBC has a WBC of 15×10^3 cells/mm³. Which is best for this patient?
- Admit patient for monitoring; no antibiotics are required at this time.
 - Admit patient for monitoring, and initiate piperacillin/tazobactam.
 - Consult surgery, and initiate ceftriaxone and metronidazole.
 - Consult surgery, and initiate cefotaxime and clindamycin.

VIII. NAUSEA AND VOMITING

- Definitions (American Gastroenterological Association)
 - Vomiting – Forceful oral expulsion of gastric contents associated with contraction of the abdominal and chest wall musculature
 - Nausea – The unpleasant sensation of the imminent need to vomit that may or may not ultimately lead to the act of vomiting
 - Regurgitation – Act by which food is brought back into the mouth without the abdominal and diaphragmatic muscular activity that characterizes vomiting
 - Retching – Spasmodic respiratory movements against a closed glottis with contractions of the abdominal musculature without expulsion of any gastric contents, called “dry heaving”
 - Rumination – Chewing and swallowing of regurgitated food that has come back into the mouth through a voluntary increase in the abdominal pressure within minutes of eating or during eating
- Pathophysiology
 - Housed in the brain stem, the vomiting center incorporates the response and activity to the muscarinic (M_1), histamine-1 (H_1), neurokinin-1, and serotonin receptors.
 - Receives input from four centers:
 - Chemoreceptor trigger zone
 - Located outside the blood-brain barrier and is influenced by triggers in the blood or CSF (cerebrospinal fluid)
 - Dopamine, M_1 , and H_1 receptors
 - Vagal afferent system
 - Receives input from and is activated by distension or irritation of the GI tract
 - Serotonin receptors
 - Vestibular system
 - Most often associated with motion sickness
 - M_1 and H_1 receptors
 - High cortical centers (CNS) – May be associated with nonanatomic sources of vomiting like behavioral or psychiatric disorders (e.g., stress-induced vomiting)
- Differential Diagnosis/Etiology (Table 18)
 - Wide differential diagnosis ranging from local GI tract lesions to systemic illnesses
 - A detailed history, including a medication and surgical history, is important to identify the cause. In addition, the type of emesis, pattern, and timing may assist the provider in identifying organic causes. Usually classified as nonbilious/bilious or bloody/nonbloody

Table 18. Distinguishing Characteristics of Vomiting and Potential Sites/Causes

Surgical origin	Acute onset, severe abdominal pain, with localized or generalized abdominal tenderness, signs of peritonitis, absent or hyperactive bowel sounds
Esophagus, stomach, first part of duodenum	Ingested food and clear or yellow
Obstruction of the intestine past the ampulla of Vater	Bilious emesis (presence of bile and is light green to dark green)
Upper GI tract bleeding, esophagitis, gastritis (acute)	Bright red blood in emesis or gastric lavage
Gastric bleeding, PUD, IBD (chronic)	Coffee-ground material in vomitus (blood has been in contact with gastric acid)
Gastric outlet obstruction (pyloric stenosis or if increased intracranial pressure)	Projectile vomiting; for increased intracranial pressure, early morning headache would also occur
Chronic disease (IBD, celiac disease, metabolic cause)	Poor weight gain or weight loss and history of vomiting
GERD or postnasal drainage	Nocturnal vomiting

PUD = peptic ulcer disease.

3. Common causes of emesis (Table 19)
4. Other causes (less common)
 - a. Rumination syndrome
 - i. Occurs in infants, those with a psychiatric disorder, or healthy adolescents/adults
 - ii. More common in females
 - iii. Presentation – Weight loss, abdominal pain, constipation, nausea, diarrhea
 - iv. Diagnosed using Rome III criteria: Must include all of the following and be present for at least 3 months; onset should have been at least 6 months before diagnosis:
 - (a) Repeated painless regurgitation and re-chewing or expulsion of food that begins soon after ingestion of a meal, does not occur during sleep, and does not respond to standard GER treatment
 - (b) Absence of retching
 - (c) No evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the symptoms
 - v. Often misdiagnosed; generally use behavior therapy for treatment, also nutrition support
 - b. Cyclic vomiting syndrome
 - i. Functional disorder, Rome IV diagnostic criteria in children and adolescents:
 - (a) Two or more periods of intense, unremitting nausea and paroxysmal vomiting, lasting hours to days within a 6-month period
 - (b) Episodes should be stereotypical in each patient.
 - (c) Episodes are separated by weeks to months, with return to baseline between episodes.
 - (d) After appropriate medical evaluation, symptoms cannot be attributed to any other condition.
 - ii. Also linked to family history or presence of migraines
 - iii. Lifestyle modifications help prevent episodes: Sleep hygiene, avoidance of triggers (e.g., fasting, caffeine, chocolate)
 - iv. Prophylactic pharmacotherapy can be used if symptoms occur more than once every other month, if patient required hospitalization, or if quality of life is being affected (see Treatment section that follows).

- c. Acute intestinal obstruction after infancy
 - i. Toddlers and older children
 - ii. Presentation – Abdominal pain, nausea, vomiting (often bilious), abdominal distension, peritonitis (if prolonged symptoms)
 - iii. Differential diagnosis
 - (a) Intussusception
 - (b) Malrotation with or without volvulus
 - (c) Incarcerated hernias
 - (d) Strictures (may result from NSAID use; irradiation; CD)
 - (e) Adhesions (postsurgical)
 - (f) Bezoars
 - (g) Superior mesenteric artery syndrome
 - (h) Small intestinal tumors (lymphoma or carcinoid)
 - iv. Prompt evaluation is warranted.
 - (a) Gastric decompression (by nasogastric tube)
 - (b) Radiologic studies
 - (c) Surgical consultation

Table 19. Causes of Nausea/Vomiting by Age Group

Age Group	Causes
Neonates and young infants	Gastroesophageal reflux • Also interchangeable with regurgitation Milk protein–induced enteritis Pyloric stenosis • May be associated with erythromycin use (rare cases of azithromycin and maternal macrolide use reported) Adrenal insufficiency Intestinal obstruction or atresia • Small intestine most common and often associated with congenital anomalies • Present with bilious emesis, abdominal distension, failure to pass meconium (“double bubble sign” on abdominal radiography) Malrotation Hirschsprung disease Inborn errors of metabolism • Rare • Can present as cyclic or recurrent vomiting • Includes: Mitochondrial, fatty acid oxidation disorders, urea cycle defects, organic acidurias

Table 19. Causes of Nausea/Vomiting by Age Group (*continued*)

Age Group	Causes
Older infants and children	Infections • Pharyngitis, UTIs, upper respiratory (including posttussive emesis), gastroenteritis (viral most common cause) Gastroparesis Intussusception Allergic reactions and food/environmental intolerances Adrenal crisis Intracranial hypertension Cyclic vomiting syndrome (can occur in older individuals, too) Eosinophilic esophagitis • May be linked to food allergen hypersensitivity • Presentation depends on age ◦ 1–4 yr: Feeding dysfunction, failure to thrive ◦ > 4–12 yr: Vomiting ◦ 10–15 yr: Abdominal pain, chest pain in adolescents Munchausen syndrome by proxy
Adolescents	Infections (UTI, gastroenteritis, influenza) Functional dyspepsia Appendicitis IBD Pregnancy Bulimia or psychogenic vomiting Rumination syndrome • See section notes

D. Treatment

1. Treat the underlying cause first. Some disease states discourage the use of antiemetics, and often, use of these agents is determined by the risk of continued vomiting and resulting sequelae (weight loss, dehydration, electrolyte abnormalities).
2. Specific treatments related to disease states discussed in Table 19:
 - a. GER (see GERD section)
 - b. Pyloric stenosis – Surgical correction; manage hydration status, acid-base and electrolyte imbalance
 - c. Atresias – Surgical correction and management of postsurgical nutrition, fluid/electrolytes
 - d. Gastroenteritis – Use of antiemetics is controversial because vomiting sometimes acts as a mechanism for ridding the body of the infectious organism/toxin. One meta-analysis suggested that use of ondansetron reduced need for hospitalization and intravenous fluids by reducing vomiting. Of note, ondansetron can cause diarrhea, which may worsen dehydration.
 - e. Eosinophilic esophagitis – Acid suppression, corticosteroids (topical in addition to systemic), dietary modifications
 - i. May see PPI, swallowed fluticasone (using inhaler, swallow 2 puffs, twice daily), or budesonide slurry (0.5 mg of budesonide nebulizer solution mixed with 5 packets of sweetener such as Splenda)
 - ii. Elimination diet based on allergy testing
 - f. Rumination syndrome – In addition to behavioral therapy, a PPI may be used if presence of esophagitis from emesis. Although no overwhelming supportive evidence, trials of prokinetic agent, antidepressants, baclofen have been reported

- g. Cyclic vomiting syndrome
 - i. NASPGHAN guidelines for treatment (J Pediatr Gastroenterol Nutr 2008;47:379-93)
 - ii. Prophylactic therapy (indicated if symptoms occur more than once every other month; hospitalization; quality of life affected)
 - (a) Tricyclic antidepressants (68% effective)
 - (1) Younger than 5 years – Do not use; instead, use cyproheptadine as first-line therapy
 - (2) Older than 5 years – Amitriptyline
 - (A) May add combination of carnitine
 - (B) May take a few months to be effective
 - (b) Propranolol – 87% of patients treated with propranolol had improvements in symptoms.
 - (c) Other agents (have been used for migraine therapy as well)
 - (1) Phenobarbital
 - (2) Topiramate
 - (3) Sumatriptan
 - (4) Birth control if catamenial symptoms
 - iii. Treatment during acute episodes
 - (a) Hydration, electrolyte replacement
 - (b) Ondansetron
 - (c) Sedation with diphenhydramine, lorazepam, chlorpromazine
 - (d) If abdominal pain becomes severe, may use ketorolac, but would need to balance with risk of GI bleed, possibility of GI distress (especially with renal insufficiency)
- 3. Antiemetic medications
 - a. Categorized by receptor of action
 - b. Serotonin receptor antagonists (most commonly used)
 - i. Good for chemotherapy-induced nausea and vomiting, postoperative, postirradiation
 - ii. Common adverse effects: Headache, constipation, diarrhea (ondansetron), asthenia, dizziness
 - iii. Associated with QTc prolongation and increases the risk of serotonin syndrome with the use of agents like amitriptyline
 - iv. Ondansetron: Many dosage forms, including orally disintegrating tablet, oral solution, injection, tablets
 - v. Granisetron
 - (a) Twice-daily dosing for enteral route
 - (b) Patch, injection, tablet, solution
 - vi. Dolasetron
 - (a) One-time dose
 - (b) Watch for hypomagnesemia and hypokalemia.
 - (c) Tablets, extemporaneous preparation recipe available
 - vii. Palonosetron: Long duration – 24 hours to 5 days
 - c. Dopamine receptor antagonists (anticholinergic and antihistaminergic activity as well)
 - i. Common adverse effects: Drowsiness, sedation
 - ii. Risk of QTc prolongation (need baseline ECG and if on continued therapy)
 - iii. Phenothiazines
 - (a) Promethazine – Not to be used in children younger than 2 years, extravasation risk, black box warning for severe tissue injury; Institute for Safe Medication Practices recommends removal of intravenous use
 - (b) Prochlorperazine
 - (c) Chlorpromazine
 - (d) Perphenazine
 - (e) Commonly used as antiemetics

- iv. Butyrophenones
 - (a) Droperidol
 - (b) Haloperidol
 - (c) Good for intractable emesis from gastritis
- v. Benzamides
 - (a) Metoclopramide
 - (1) Also stimulates cholinergic receptors, which leads to gastric peristalsis (also used to treat gastroparesis)
 - (2) Black box warning in the United States for tardive dyskinesia with long-term use
 - (3) Good for GER, motility disorders, but generally avoided in younger patients
 - (b) Domperidone
 - (1) Selective to upper GI tract
 - (2) No CNS effects because it does not cross the blood-brain barrier
 - (3) Not available in the United States
 - (c) Common adverse effects: Extrapyramidal reactions (treat with diphenhydramine) and drowsiness
- d. H_1 receptor antagonists (antihistamines)
 - i. Cyclizine
 - ii. Hydroxyzine
 - iii. Diphenhydramine: Many dosage forms (injection, tablet, and solution)
 - iv. Dimenhydrinate
 - v. Common adverse effects: Sedation, dry mouth
- e. Muscarinic receptor antagonists
 - i. Scopolamine
 - ii. Used as prophylactic agent for motion sickness
 - iii. Available as a patch; do not cut (may occlude backing, but not recommended); 72-hour duration
- f. Benzodiazepines
 - i. Lorazepam
 - ii. Diazepam
 - iii. Midazolam
 - iv. Good for chemotherapy, cyclic vomiting
 - v. Common adverse effect: Sedation
- g. Neurokinin receptor antagonists
 - i. Block substance P-mediated nausea and vomiting
 - ii. Aprepitant (oral)
 - iii. Fosaprepitant (intravenous)
 - iv. Used for chemotherapy-induced nausea and vomiting (particularly highly emetogenic agents like cisplatin). Efficacy enhanced with concomitant use of serotonin receptor antagonist and dexamethasone
 - v. Drug interactions with birth control and warfarin (also inhibitor of CYP3A4)
- h. Cannabinoid receptor agonist
 - i. Dronabinol
 - ii. Used for chemotherapy-induced nausea and vomiting if other agents are ineffective
 - iii. Common adverse effects: Appetite stimulation, euphoria, cognitive impairment
- i. Motilin agonist (macrolide antibiotics)
 - i. Erythromycin (most common)
 - ii. Good for gastroparesis or other motility disorder
 - iii. Common adverse effects: Diarrhea, nausea
 - iv. May increase QTc with prolonged use
 - v. Drug interactions – Acts as a CYP3A4 inhibitor

Patient Case

11. A 3-week-old boy presents with projectile vomiting and bilious emesis. The patient has had no sick contacts, and no formula changes have been made. The abdominal radiograph is read as normal. Current laboratory values show a normal CBC and the following basic metabolic panel: sodium 139 mEq/L, potassium 4 mEq/L, chloride 98 mEq/L, bicarbonate 35 mEq/L, BUN 20 mg/dL, and SCr 0.6 mg/dL. Which is the most likely cause of this infant's vomiting?
- A. Acute gastroenteritis.
 - B. Duodenal atresia.
 - C. GERD.
 - D. Pyloric stenosis.

IX. ULCERS**A. Definition and Classification**

1. Gastritis – “Precursor” lesion to mucosal ulceration; important cause of abdominal pain in children
2. Peptic ulcer – Sharply circumscribed loss of the tissue lining the stomach or duodenum
 - a. Primary – Usually duodenal; occurs in otherwise healthy children
 - i. Gastric ulcers are becoming more common in children.
 - ii. Mucosal inflammation and ulceration can be caused by *Helicobacter pylori* (gram-negative microaerophilic rod) – Most children have asymptomatic infections that never develop into clinically evident disease.
 - b. Secondary – Usually associated with underlying systemic disorders, especially medication use
 - i. Head trauma, sepsis, drug ingestion
 - ii. Gastroduodenal ulcers can also occur with specific diseases – Zollinger-Ellison syndrome or CD
 - iii. Uncommon – Link to cystic fibrosis and sickle cell disease
 - iv. Acute medical emergencies with hemorrhage and/or perforation
 - v. High mortality (14%–58%)

B. Pathogenesis/Etiology

1. Rare in children; however, in children older than 2 years, primary ulcers are more common.
2. Both duodenitis and gastritis play a potential role in ulcer development by increasing epithelial cell exposure to hydrochloric acid. Gastric acidity is lower with gastric ulcers and higher with duodenal ulcers.
3. Toxic mechanisms include:
 - a. Acid
 - b. Pepsin
 - c. Medication (aspirin, NSAIDs)
 - d. Bile acids
 - e. Infection with *H. pylori*
4. Signs/symptoms by location
 - a. Gastric ulcer – Pain is worsened by eating.
 - b. Duodenal ulcer – Eating relieves pain.

Table 20. Symptomatic Criteria for Dyspepsia

Child must have symptoms for at least 2 mo

Must have: both major criteria, one major as well as two minor, or four minor criteria (would warrant referral to gastroenterologist)

Major Criteria	Minor Criteria
Epigastric abdominal pain Recurrent vomiting (at least 3 x/mo)	Anorexia/weight loss Pain that awakens child at night Heartburn Oral regurgitation Chronic nausea Excessive belching/hiccupping Early satiety Periumbilical abdominal pain Family history of PUD, dyspepsia, or IBS

C. Diagnosis/Evaluation

1. History and physical examination
 - a. Evaluate signs/symptoms in Table 20.
 - b. Receipt of causative medications (NSAIDs, corticosteroids)
 - c. Check dosing of H₂RAs – Often, lack of response because of inadequate dosing or frequency
2. Endoscopy
 - a. Warranted if there is GI bleeding; odynophagia; refusal to eat; persistent, unexplained vomiting; or if abnormalities are revealed on upper GI radiographic series
3. Testing for *H. pylori*
 - a. Not recommended in children with functional abdominal pain. May be considered in children with:
 - i. First-degree relatives with gastric cancer
 - ii. Refractory iron-deficiency anemia (other causes ruled out)
 - b. For initial diagnosis, should use either a positive histopathology plus a positive rapid urease test or a positive culture
 - c. Validated ELISA test is reliable for eradication testing of *H. pylori* (stool testing).
 - d. Serologic tests for IgG antibody titers are available for adults, but the sensitivity and specificity of these tests vary in children.
 - e. 13C-urea breath test – Noninvasive, easy to perform and repeat
 - i. Measures bacterial colonization in gastric mucosa
 - ii. Is considered a reliable test for eradication of *H. pylori*
 - f. Recommended to wait at least 2 weeks after discontinuing PPI therapy and 4 weeks after antibiotics to perform biopsy-based and noninvasive tests for *H. pylori*

D. Treatment (non-*H. pylori*)

1. First line: H₂RAs
 - a. Famotidine; more rarely used: cimetidine
 - b. Decrease volume of gastric secretions and amount of gastric acid
2. Second line: PPIs (after no response to H₂RAs)
 - a. Omeprazole, lansoprazole are used more commonly
 - b. Irreversible inhibitors of H⁺/K⁺-ATPase
3. Cytoprotective agents may be useful if mucosal lesions are present. Sucralfate is a sucrose octasulfate and polyaluminum hydroxide complex that forms a sticky gel that adheres to injured mucosa at a pH of less than 4. Use is often limited by drug and food interactions.

4. Anticholinergic agents are rarely used.
 - a. Atropine, imipramine – Generally not effective as a single agent
 - b. In adult studies, anticholinergics augment the effect of H₂RAs in those with duodenal ulcers.
- E. Treatment of *H. pylori* Infections (Table 21) (J Pediatr Gastroenterol Nutr 2017;64:991-1003)
 1. Eradication is recommended in pediatric patients with peptic ulcer disease (PUD).
 - a. In the absence of PUD (but positive detection on biopsy), treatment may be considered.
 - b. Test and treat strategy not recommended in children
 - c. If a child has *H. pylori* and a first-degree relative has gastric cancer, treatment may be offered.
 2. Eradication regimens have an 87%–95% success rate in children.
 3. Antibiotic susceptibility testing for clarithromycin is recommended before using clarithromycin-based triple therapy if performed in an area having greater than 20% resistance.
 4. Duration should be 7–14 days.
 5. Reliable, noninvasive test for eradication recommended at least 4–8 weeks after completion of therapy
 6. If treatment failure, consider the following:
 - a. Perform an EGD (esophagogastroduodenoscopy) with culture and susceptibility testing.
 - b. FISH (fluorescence in situ hybridization) testing on previous biopsies to test for clarithromycin resistance (if not performed before)
 - c. Modification of therapy
 - i. Add an antibiotic, or change antibiotics.
 - ii. Add bismuth.
 - iii. Increase the dose and/or duration of therapy.

Table 21. Three Combinations for Eradicating *H. pylori* in Children

Amoxicillin 50 mg/kg/day (max 2 g/day) divided BID x 7–14 days plus Clarithromycin 15 mg/kg/day divided BID x 7–14 days plus PPI 1 mg/kg/day divided BID x 1 mo	Amoxicillin 50 mg/kg/day (max 2 g/day) divided BID x 7–14 days plus Metronidazole (max 1 g/day) 20 mg/kg/day divided BID x 7–14 days plus PPI 1 mg/kg/day divided BID x 1 mo	Amoxicillin 50 mg/kg/day (max 2 g/day) divided BID x 7–14 days plus Metronidazole (max 1 g/day) 20 mg/kg/day divided BID x 7–14 days plus Bismuth salt (bismuth subsalicylate or subcitrate)** 8 mg/kg/day divided QID (alternative dosing: children ≤ 10 yr: 15 mL (262 mg) QID for 6 wk; children > 10 yr: 30 mL (525 mg) or two 262-mg tablets QID x 6 wk) **Avoid bismuth in the presence of renal failure.

In patients with penicillin allergy:

Adults: Bismuth quadruple therapy has been described using PPI, bismuth salt, tetracycline, and metronidazole; eradication rates with this regimen were better than with PPI, clarithromycin, metronidazole or PPI, clarithromycin, and levofloxacin regimens

Children: A combination of clarithromycin, metronidazole, and PPI has been used as first-line therapy

May also consider testing for true penicillin allergy

Patient Case

12. A 9-year-old African American boy (weight 30 kg) presents with a 2-month history of epigastric abdominal pain, weight loss, and chronic heartburn. He has been taking OTC calcium carbonate 500 mg with each meal and famotidine 40 mg/day, but with only temporary relief. Eating does not seem to help relieve the pain or heartburn. Which is best for this patient?
- A. Famotidine 20 mg orally twice daily.
 - B. Lansoprazole 30 mg orally daily.
 - C. Sucralfate 500 mg orally four times daily.
 - D. Famotidine 20 mg orally twice daily plus imipramine 25 mg at bedtime.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

This patient is a “happy spitter.” Although he has some irritability, no warning signs are present, and he is maintaining adequate growth. Overfeeding may be an issue, so patient education and correction of feeding practices would be the best recommendation at this time (Answer A is correct). An anti-regurgitation formula (Answer B is incorrect) might be warranted if the child continued to have symptoms after adjusting volume. Answers C and D are incorrect because neither antisecretory nor promotility agents are recommended for physiologic infant regurgitation.

2. Answer: B

Obesity, which is likely a contributing factor to this patient’s reflux, should be managed; moreover, because of the increasing frequency and pain associated with the patient’s episodes, a 4- to 8-week trial of a PPI is warranted (Answer B is correct). Either therapy alone would not be as effective; therefore, the combination would be the most appropriate, making Answers A and C incorrect. Famotidine (Answer D) is recommended for occasional heartburn, but because this patient has recurrent symptoms, famotidine would not be the best therapy.

3. Answer: C

Patients with cystic fibrosis are at an increased risk of *C. difficile*, and this patient has had recent (and current) antibiotic exposure. Answer A is incorrect because discontinuing antibiotics would not be optimal in this patient population. Although both metronidazole and vancomycin are options for an initial episode, the intravenous route would not be recommended in a patient with more moderate symptoms, making Answer B incorrect. Answer C is correct; oral vancomycin or oral metronidazole is recommended for a nonsevere initial episode. Answer D is incorrect because fidaxomicin is usually reserved for toxic megacolon and refractory cases after several trials with oral metronidazole and vancomycin.

4. Answer: C

For disimpaction therapy, polyethylene glycol is recommended first line (Answer C). Bisacodyl suppositories (Answer A), although a second-line agent, would not be recommended for disimpaction because the rectal formulation might be inserted into the middle of the

stool, preventing it from coming into contact with the mucosa. Magnesium hydroxide (Answer B) is used for maintenance therapy, and contrast enemas (Answer D) are only recommended for intractable constipation.

5. Answer: B

Answers A, C, and D—IBS-C, IBS-M, and patient does not meet the criteria for IBS—are incorrect because according to this patient’s symptoms, she meets the criteria for IBS-D (Answer B is correct). She has had symptoms for 6 months, and the stools change appearance (soft and mushy) when she has abdominal pain and headache. These symptoms occur five times per month. According to the Bristol Stool Form Scale, she primarily has type 6, which would give her the subclassification of IBS-D.

6. Answer: D

In a patient with IBS, the goals of therapy include a return to a normal bowel function, elimination of symptoms, and improvement in quality of life. However, this is often unachievable by medications alone. Answer A is incorrect because avoiding gluten in the absence of celiac markers is not helpful. Ibuprofen (Answer B), which may aggravate symptoms, should not be used for pain in patients with IBS. Answer C is incorrect; although fluoxetine would help regulate GI motility, it is often used in IBS-C because the adverse effect can be diarrhea. Amitriptyline (Answer D) would be a reasonable choice because it is effective in IBS-D and would help with the patient’s other symptoms as well.

7. Answer: B

This patient’s disease would be considered refractory because maintenance therapy did not prevent two courses of corticosteroid therapy. Azathioprine (Answer A) is used for maintenance therapy, not induction. Answer C is incorrect because mesalamine would be used for induction in mild to moderate, not severe, disease. Answer D is incorrect because methotrexate is generally used for maintenance therapy, and there are data on infliximab (Answer B) use for both induction and maintenance.

8. Answer: B

According to this patient's symptoms, she has mild disease. Rectal mesalamine therapy (Answer A) would not be appropriate because the disease extends beyond the rectum. Oral mesalamine is used for initial treatment with mild disease (Answer B). Because of the patient's sulfa allergy, Answer C, sulfasalazine, would not be recommended, although it would otherwise be a choice for initial treatment. Answer D is incorrect because intravenous corticosteroids would be indicated for initial therapy in severe disease.

9. Answer: C

Answer C is correct because sodium replacement is often needed to account for increased losses after surgery, especially with an ostomy. Answer A is incorrect because central access is preferred in patients with SBS receiving PN, allowing higher dextrose and calcium concentrations to be used. Initial dextrose management in PN should not be at the goal dextrose infusion rate. A gradual increase will prevent hyperglycemia, often a problem in postoperative management. Answer B is incorrect; H₂RAs may be useful in the early phase after resection, during which gastric hypersecretion may occur, leading to decreased fat absorption and bacterial overgrowth. Answer D is incorrect because antimotility agents should not be considered until bowel adaptation has occurred and enteral feeding has been initiated. Pharmacologic therapy for increased motility should be carefully considered and initiated only if adequate growth or caloric needs cannot be attained.

10. Answer: C

According to the Pediatric Appendicitis Scoring Tool, this patient is considered at high risk of appendicitis, and admission with surgical consult is warranted. The need for appendectomy would be assessed with further diagnostic imaging and clinical response. Antibiotic therapy would need to be initiated because of the patient's high-risk status, making Answer A incorrect. The IDSA guidelines report the success of single, dual, and triple therapy. However, this patient was previously healthy and would not need pseudomonal coverage with piperacillin/tazobactam (too broad) at this time (Answer B). Answer D is incorrect; although cefotaxime is considered appropriate, clindamycin should be avoided because of resistance. However, ceftriaxone and metronidazole would be an appropriate initial antibiotic regimen (Answer C is correct).

11. Answer: D

This patient has presented with the classic symptoms of pyloric stenosis—bilious emesis, projectile vomiting, and a hypochloremic metabolic alkalosis (Answer D). Answer A is incorrect because the patient has had no sick contacts to suggest gastroenteritis. Answer B is incorrect because the abdominal radiograph does not reveal duodenal atresia (would reveal the double bubble sign). Gastroesophageal reflux (Answer C) is a likely cause in an infant, but this patient's symptoms are much more severe than regurgitation or reflux.

12. Answer: B

This patient, whose OTC therapy has failed, meets the criteria for dyspepsia. Because his pain is unrelieved by eating, a gastric ulcer is likely. Answer A is incorrect because the patient has already tried an H₂RA and the dose was maximized, so changing to another H₂RA would not be beneficial. Without imaging to see whether lesions are present, sucralfate (Answer C) would not be the initial therapy choice. Answer D is incorrect; although the combination of an anticholinergic and an H₂RA has been studied in adults, the benefit of this combination has only been shown in treating duodenal ulcers. After no response to H₂RAs, a PPI is second line (Answer B). This patient would also benefit from referral to a gastroenterologist for further workup.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

In children and adolescents with recurrent heartburn, a 2- to 4-week trial of a PPI is warranted (Answer C). No evidence supports eliminating a food from the diet, making Answer A incorrect. Because this patient has tried OTC calcium carbonate and the patient's symptoms have lasted for 2 months, an H₂RA (Answer B) would probably not be effective at this time. Therapy with an H₂RA would be recommended for occasional heartburn symptoms. At this time, the patient's symptoms do not warrant referral to a gastroenterologist (Answer D). If, after 3 months, the heartburn persists on PPI or recurs after therapy is discontinued, a referral would be recommended.

2. Answer: B

This patient likely has diarrhea secondary to gastroenteritis. Answer A is incorrect; although there may be a transient lactose intolerance with gastroenteritis, changing to a soy formula is not recommended. The patient's degree of dehydration seems to be moderate, and the patient is taking some oral feeds, making Answer B an appropriate choice. Intravenous fluid replacement (Answer C) would be indicated for severe dehydration, and oral replacement has been shown to be as effective as intravenous replacement in mild to moderate dehydration. Answer D is incorrect because an antidiarrheal would not be recommended for acute gastroenteritis or for an individual this age.

3. Answer: D

Given this patient's clinical presentation, he meets the Rome III criteria for constipation. Treatment for impaction is needed, so glycerin (Answer A) would not be a good option (glycerin is good for maintenance/prevention). Answer B is incorrect because although docusate sodium would offer stool-softening properties, it is indicated for the prevention of constipation, not as a sole agent for the treatment of impaction. Although mineral oil (Answer C) would treat impaction, it would not be recommended in this age group or in the presence of neurologic dysfunction (risk of aspiration). Answer D, polyethylene glycol, is correct because this is the recommended first-line therapy for disimpaction. Polyethylene glycol has a relatively safe adverse effect profile; however, its use would warrant electrolyte evaluation, and it would be contraindicated if this patient were to have a bowel obstruction.

4. Answer: A

This patient meets the diagnostic criteria for IBS-C. Although food avoidance has not directly been recommended in the treatment for IBS, the avoidance of high-fat foods would probably be helpful in this patient. Answer A, adding stress management and relaxation techniques with the initiation of psyllium therapy, would be the most appropriate and comprehensive treatment strategy for this patient. Providing fiber in its soluble form (e.g., psyllium) is considered first line for IBS-C. Answer B is not optimizing therapy by continuing diet and only gradually increasing dietary fiber. Answers C and D are incorrect because they involve the use of laxatives, which would be recommended as second-line therapy, and use of the antidepressant citalopram in Answer D would not be recommended at this time and should be discussed further with the patient's provider.

5. Answer: C

Use of Answer A, methotrexate, in children with CD is less established than in adults, and methotrexate is usually considered for maintenance therapy, not induction. Moreover, the oral route may be less preferred than the subcutaneous route for therapy initiation because of concern for more erratic absorption. Some clinicians will begin with subcutaneous methotrexate and then change to oral therapy if the patient is adherent. Answer B is incorrect because, according to the Pediatric Crohn's Disease Activity Index score, this child has moderate to severe CD; therefore, mesalamine would not be recommended. Mercaptopurine (Answer D) is used in maintenance therapy, and prednisone is the drug of choice for induction in severe cases. If this patient were unable to tolerate an oral trial of prednisone (Answer C), intravenous methylprednisolone would be warranted. Of note, EEN has been used for severe CD induction therapy. Although EEN is currently recommended by the ESPGHAN as potential first-line therapy, most clinicians aim for a rapid remission induction, and it can take weeks to see the effects of EEN.

6. Answer: B

This patient with documented moderate disease has responded to steroids. Prednisone (Answer A) would be used for initial or induction therapy, not maintenance.

An aminosalicylate agent would be the best therapy at this time. Mesalamine (Answer B) would be preferred to sulfasalazine (Answer C) because of the patient's possible allergy to sulfa (the patient has a documented allergy to Bactrim). Answer D is incorrect because azathioprine is reserved for steroid-dependent disease.

7. Answer: B

This patient's diarrhea is secondary to SBS, probably caused by initiation of feeds. The diarrhea is refractory to initiating low-volume, continuous feeds. Discontinuing diphenoxylate/atropine (Answer B) is correct; if no improvement occurs after around 48 hours of use, diphenoxylate/atropine should be discontinued because it will unlikely be effective. Answer A is incorrect because increasing the dose above the recommended range would potentially cause additional adverse effects with little change in efficacy. Octreotide (Answer C) is incorrect because it is generally reserved for patients with diarrhea secondary to graft-vs.-host disease or secretory diarrhea and has few data supporting routine use. Ursodiol (Answer D) is incorrect because the patient is not reported to have cholestasis and is only receiving low-volume feeds. Ursodiol should not be initiated for PN-associated liver disease until the patient is on full, or close to full, feeds (hyperosmolar solution).

8. Answer: C

This patient's diarrhea with irritation is likely a result of decreased bile acid absorption from extensive ileal resection. Answer A is incorrect because the patient has been able to tolerate progress of enteral feeds, and unless she is losing weight, increasing PN will not be beneficial. Answer B is incorrect; although vitamin B₁₂ can be deficient in this population, the acute issue is the diarrhea and resulting malabsorption. (Of note: Although not validated in pediatric patients, patients should also have a methylmalonic acid concentration obtained with the B₁₂ concentration, especially patients younger than 5 years for whom reference ranges for serum B₁₂ concentrations are lacking.) Answer C, adding cholestyramine, would help decrease the diarrhea associated with increased bile acids, which is also likely causing skin irritation. Loperamide (Answer D) would be an option for diarrhea if it becomes chronic, but more information on the patient's age and clinical status is needed. Loperamide can also cause bacterial overgrowth, which may worsen malabsorption.

9. Answer: C

Because this patient has perforated appendicitis, antibiotics should be continued postoperatively, making Answer A incorrect. Answer B is incorrect because clindamycin should be avoided, given increasing resistance. Although single-agent therapy (Answer D) has been used, this patient appears to have no risk factors for resistance that would warrant use of a carbapenem. The best choice for this patient would be ceftriaxone and metronidazole (Answer C), which would provide coverage for the gram-negative and anaerobic organisms involved (similar to the recommendations in the IDSA guidelines for community-acquired intra-abdominal infections).

10. Answer: B

This patient has cyclic vomiting, for which prophylactic therapy is recommended if symptoms occur more than once every other month, patients are hospitalized, or quality of life is affected. Tricyclic antidepressants are usually recommended as first-line therapy. Cyproheptadine is recommended for patients younger than 5 years, whereas amitriptyline is recommended for those older than 5 years. This patient is 4 years old, so amitriptyline (Answer A) would not be the best choice, making cyproheptadine the best answer (Answer B). Diphenhydramine (Answer C) has been used for sedation during acute episodes but would not be used for prophylactic therapy. Answer D is incorrect because ketorolac would also be used during an acute episode for severe abdominal pain, not for prophylaxis.

11. Answer: B

Answer A is incorrect because eradication therapy is recommended for a patient with PUD and a family history of gastric cancer. A three-agent regimen is recommended, which should always include amoxicillin, making Answer D incorrect. Answer C is incorrect because a PPI is recommended (or bismuth salt), not sucralfate. Sucralfate may also inhibit nutrient absorption. When choosing between clarithromycin and metronidazole, metronidazole is the better choice if the suspected resistance to clarithromycin is greater than 20%. Answer B is correct because it includes three agents—amoxicillin, clarithromycin, and a PPI—and there is no indication for clarithromycin resistance.

12. Answer: A

This patient would be considered a healthy infant with uncomplicated recurrent regurgitation. Because he had

adequate weight gain and nutrition status, changing the formula (Answer B) would not be recommended, but parental education and encouragement would be appropriate for this patient (Answer A). Answers C and D are incorrect because antisecretory therapy is not recommended unless other complications occur from symptoms.

13. Answer: B

According to this patient's history, he has not been maintained on polyethylene glycol (first-line therapy for maintenance therapy). Lactulose (Answer B), the recommended second-line therapy, is generally well tolerated in children. Answer A is incorrect because bisacodyl is not recommended for daily use. Magnesium citrate (Answer C) would not be used for maintenance therapy. Answer D is incorrect; although senna may be used as a second-line agent, the dosing is incorrect for this patient's age.

INFECTIOUS DISEASES

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**UNIVERSITY OF FLORIDA COLLEGE OF PHARMACY,
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Learning Objectives

1. Determine appropriate treatment for pediatric patients with respiratory tract infections, central nervous system (CNS) infections, soft tissue infections, bone and joint infections, urinary tract infections, (UTIs) intra-abdominal infections, and endocarditis.
2. Describe appropriate first-line treatment of fungal infections, tuberculosis, and parasitic infections in pediatric patients.
3. Identify appropriate surgical prophylactic strategies for pediatric patients.
4. Determine appropriate prophylactic agents for pediatric patients with respiratory tract infections and CNS infections.

Abbreviations

AOM	Acute otitis media
CA-MRSA	Community-acquired methicillin-resistant <i>Staphylococcus aureus</i>
CBC	Complete blood count
CNS	Central nervous system
CRP	C-reactive protein
CSF	Cerebrospinal fluid
CT	Computed tomography
ED	Emergency department
ESR	Erythrocyte sedimentation rate
GAS	Group A <i>Streptococcus</i>
Hib	<i>Haemophilus influenzae</i> type b
HSV	Herpes simplex virus
MIC	Minimum inhibitory concentration
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>
PCR	Polymerase chain reaction
PPD	Purified protein derivative
RADT	Rapid antigen detection test
RSV	Respiratory syncytial virus
STD	Sexually transmitted disease
TB	Tuberculosis
TM	Tympanic membrane
UTI	Urinary tract infection
VUR	Vesicoureteral reflux
WBC	White blood cell count

Self-Assessment Questions

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

1. T.G. is a 10-month-old boy (weight 10 kg) who presents to the clinic with a 3-day history of fever (temperature 38.5°C), increased fussiness, decreased appetite, and increased lethargy. He has also been pulling on his right ear. Examination of both ears reveals that each has a bulging, erythematous, nonmobile tympanic membrane (TM). He cooperates with the examination and does not seem to experience pain on manipulation of his ears, just discomfort. His medical history is noncontributory. He has no history of antibiotic use and no drug allergies. He has two older siblings and attends day care 3 days a week. Which treatment option is most appropriate to recommend for T.G.?
 - A. Amoxicillin/clavulanate 400 mg orally twice daily.
 - B. Amoxicillin 450 mg orally twice daily.
 - C. Ceftriaxone 750 mg intramuscularly once.
 - D. Observation plus pain management × 48 hours.
2. A 12-year-old girl (weight 50 kg) presents to the emergency department (ED) 2 days after someone kicked her in the shin while playing soccer. Her lower leg is red and erythematous. She has limited mobility of her toes and cannot bear weight on her leg. She also has a temperature of 40°C. Radiography reveals soft tissue swelling consistent with cellulitis. Which is the best antibiotic regimen to initiate empirically in the ED?
 - A. Doxycycline 100 mg intravenously once.
 - B. Nafcillin 2000 mg intravenously once.
 - C. Ampicillin/sulbactam 1500 mg intravenously once.
 - D. Meropenem 1000 mg intravenously once.
3. B.L. is a 2-year-old girl (weight 15 kg) with a history of reactive airway disease who presents to the ED with a 2-day history of wheezing, cough, and runny nose. Today, she has increased work of breathing with continued wheezing that did not respond to albuterol at home; she says that her “muscles hurt.” A respiratory viral panel is positive for influenza A. The patient is to be admitted for

treatment of an asthma exacerbation. Which agent would also be best to initiate on admission?

- A. Zanamivir.
- B. Amantadine.
- C. Ribavirin.
- D. Oseltamivir.

4. K.M. is a 21-month-old girl admitted to the hospital with a 3-day history of fussiness, decreased appetite, and high temperature (40°C). Meningitis is suspected, and a lumbar puncture reveals the following: white blood cell count (WBC) 8×10^3 cells/mm³ (72% segs, 15% bands, 11% lymphs), glucose 22 mg/dL, and protein 95 mg/dL. The Gram stain also reveals the presence of gram-positive cocci. The patient is placed on empiric therapy with vancomycin and ceftriaxone. Three days later, her cerebrospinal fluid (CSF) grows *Streptococcus pneumoniae* with the following sensitivities:

Penicillin	R
Rifampin	S
Ceftriaxone	S
Vancomycin	S

Which would be the most appropriate change to K.M.'s antibiotic regimen, given these culture and sensitivity results?

- A. Continue vancomycin and ceftriaxone.
 - B. Discontinue ceftriaxone, continue vancomycin, and add rifampin.
 - C. Discontinue vancomycin and continue ceftriaxone.
 - D. Discontinue vancomycin, continue ceftriaxone, and add rifampin.
5. A.C. is a 6-year-old boy (weight 30 kg) who presents to a local ED (local community-acquired methicillin-resistant *Staphylococcus aureus* [CA-MRSA] resistance 15%, local clindamycin resistance 5%) with left lower leg pain and swelling and the inability to bear weight for the past week, together with acute onset of fever and malaise during the past 3 days. His medical history is also significant for the upper respiratory symptoms of rhinorrhea, cough, and postnasal drip. On examination, there is diffuse tenderness and limited movement. The patient has had no recent trauma.

Which is the best empiric antibiotic regimen to initiate on admission for suspected osteomyelitis?

- A. Cefazolin 750 mg intravenously every 8 hours plus clindamycin 300 mg intravenously every 6 hours.
 - B. Ceftriaxone 1500 mg intravenously every 24 hours plus clindamycin 300 mg intravenously every 6 hours.
 - C. Ceftriaxone 1500 mg intravenously every 24 hours plus vancomycin 450 mg intravenously every 6 hours.
 - D. Cefazolin 750 mg intravenously every 8 hours plus vancomycin 450 mg intravenously every 6 hours.
6. B.F. is a 16-year-old patient admitted for management of worsening lower leg cellulitis. Three days ago, he slammed his leg in a car door, and during the past 12 hours, his leg has become much worse. His leg is warm, erythematous, edematous, and painful to the touch. Empiric antibiotics are initiated on admission. There is concern for necrotizing fasciitis because the area of cellulitis is also firm on palpation and appears to have an area of necrosis. He undergoes surgery for debridement of the necrotic area. A Gram stain of the skin tissue reveals gram-positive cocci in chains. Which antibiotic therapy would be best to initiate in this patient?
- A. Vancomycin.
 - B. Penicillin G.
 - C. Penicillin G plus clindamycin.
 - D. Clindamycin.
7. E.P. is an 18-month-old girl who presents to the ED in respiratory distress. She has a 3-day history of fever, rhinorrhea, and a "barky" cough. Inspiratory stridor is heard on examination. Which treatment regimen is most appropriate for this patient in the ED?
- A. Humidified O₂, racemic epinephrine, and nebulized budesonide.
 - B. Humidified O₂, racemic epinephrine, dexamethasone, and nebulized budesonide.
 - C. Humidified O₂, racemic epinephrine, and dexamethasone.
 - D. Humidified O₂ and racemic epinephrine.

8. K.A. is a 2-year-old who presents to the ED because of failed outpatient management of a UTI. Initially, she presented with a 2-day history of vomiting, decreased oral intake, decreased wet diapers, increased fussiness, and a 1-day history of fever (maximum temperature 39.4°C). A urinalysis revealed large leukocyte esterase, negative nitrites, and moderate blood. She has no significant medical history and no history of a UTI. She was given a dose of ceftriaxone and a prescription for cefdinir to complete at home. Forty-eight hours later, she returns to the ED with the same symptoms. She is admitted for intravenous antibiotics for 7 days. Which treatment approach is most recommended for this patient?
 - A. Renal bladder ultrasonography.
 - B. Vesicoureteral voiding cystography.
 - C. Initiation of sulfamethoxazole/trimethoprim 2 mg/kg/dose orally once daily for 6 months.
 - D. Urine culture by suprapubic aspiration.
9. K.D. is a 9-month-old boy, born prematurely at 32 weeks' gestation, with a medical history significant for necrotizing enterocolitis resulting in short gut syndrome and chronic total parenteral nutrition use. He currently has a Broviac catheter that has been in place for 4 months. Today, he presents with a 2-day history of fever, fussiness, and lethargy. Blood and urine cultures are obtained in the ED, and he is admitted for a sepsis workup. The blood cultures from both the central catheter and a peripheral line obtained in the ED reveal gram-positive cocci in clusters about 12 hours after obtaining the cultures. A transthoracic echocardiogram reveals a vegetation on the tricuspid valve. Which would be the most appropriate empiric regimen for K.D.?
 - A. Penicillin G.
 - B. Vancomycin.
 - C. Ampicillin.
 - D. Ceftriaxone.
10. L.M. is a 5-month-old girl, born prematurely at 29 weeks' gestation, with a medical history significant for necrotizing enterocolitis, several bowel resections, and jejunostomy reversal. She receives total parenteral nutrition through a Broviac catheter and takes enteral feedings. She presents to the ED with fever (temperature 39.6°C), irritability, and increased work of breathing. She is to be admitted for a sepsis workup and initiated empirically on ceftriaxone 50 mg/kg/dose intravenously once daily. On hospital day 2, the culture from her Broviac catheter is growing coagulase-negative *Staphylococcus*. Peripheral cultures have remained negative. Which is the most appropriate regimen for L.M.?
 - A. Vancomycin for 5–7 days plus catheter removal.
 - B. Vancomycin plus rifampin for 5–7 days.
 - C. Vancomycin plus vancomycin antibiotic lock therapy for 10–14 days.
 - D. Vancomycin plus gentamicin for 10–14 days plus catheter removal.
11. T.G. is a 16-year-old female adolescent who presents to her primary care physician's office with recurrent cough during the past month and new onset of fever, chills, and night sweats. She is not sexually active and has no recent history of international travel. She lives at home with her mother, stepfather (who was recently released from prison), and four siblings. A chest radiograph reveals a cavitary lesion in the right upper lobe. A tuberculin skin test (purified protein derivative [PPD]) is placed, which becomes positive (15 mm) in 24 hours. Which regimen would be best to initiate in T.G.?
 - A. Isoniazid plus rifampin.
 - B. Rifampin plus isoniazid plus pyrazinamide plus ethambutol.
 - C. Rifampin plus pyrazinamide.
 - D. Isoniazid plus rifampin plus clarithromycin.
12. C.A. is a 13-year-old female adolescent (weight 56 kg) who presents to the ED with a 1-day history of fever and severe lower right quadrant pain. On examination, she is tearful and reports a pain score of 9/10. She has rebound tenderness when palpating her abdomen. Her temperature is 39.5°C. She has no significant medical history but did begin her menses 3 days ago for the first time. Which is the best initial empiric antibiotic regimen to begin for a suspected intra-abdominal infection?
 - A. Cefazolin 1 g intravenously every 8 hours and metronidazole 500 mg intravenously every 8 hours.

- B. Ampicillin 2 g intravenously every 8 hours and gentamicin 5 mg/kg/dose intravenously every 24 hours.
- C. Ceftriaxone 2 g intravenously every 24 hours and tobramycin 5 mg/kg/dose intravenously every 24 hours.
- D. Clindamycin 600 mg intravenously every 8 hours and gentamicin 5 mg/kg/dose intravenously every 24 hours.

I. LOWER RESPIRATORY TRACT INFECTIONS

A. Influenza

1. Signs and symptoms
 - a. Common symptoms include fever, malaise, myalgia, nonproductive cough, sore throat, and rhinitis.
 - b. Coinfections with pneumococcal pneumonia or CA-MRSA pneumonia are common.
 - c. May present with empyema (collection of pus within the pleural cavity)
2. Treatment
 - a. Antiviral treatment should be initiated as soon as possible for maximum benefit in pediatric patients with documented or suspected influenza who meet the following criteria:
 - i. Hospitalized patients with confirmed influenza
 - ii. Outpatients with severe symptoms or progression of illness
 - iii. Outpatients at high risk of influenza complications
 - (a) Immunocompromised patients and those receiving immunosuppressive medications
 - (b) Those younger than 5 years
 - (c) Patients with chronic medical conditions (pulmonary, renal, hematologic, neurologic, HIV, malignancy)
 - (d) Patients receiving long-term aspirin or salicylate-containing medications
 - (e) Patients with conditions that compromise respiratory function or handling of secretions
 - iv. Children younger than 2 years
 - b. Treatment should not be delayed while confirmatory rapid diagnostic test results are pending.
3. Preexposure chemoprophylaxis can be considered in institutional outbreaks and for the following high-risk patients:
 - a. Children 3 months and older with a contraindication to influenza vaccination
 - b. Children 3 months and older who have received a hematopoietic stem cell transplant (in the first 6–12 months after transplantation) or a lung transplant
4. Antiviral agents
 - a. See dosing recommendations in Table 1.
 - b. Oseltamivir
 - i. Used for both treatment (5 days) and postexposure prophylaxis (5–7 days)
 - ii. Recommended first line antiviral agent for patients with severe, complicated, or progressive illness and all hospitalized patients
 - iii. Available as an oral suspension and a capsule
 - c. Zanamivir
 - i. Used for both treatment (5 days) and chemoprophylaxis (5–7 days)
 - ii. Approved for use in children 7 years or older for treatment and 5 years or older for chemoprophylaxis
 - iii. Available as an oral inhalation
 - d. Peramivir
 - i. Used for treatment only (one dose)
 - ii. Dose must be adjusted in renal impairment.
 - iii. Available as an intravenous infusion
 - e. Baloxavir marboxil
 - i. Used for treatment (one dose) and chemoprophylaxis (one dose)
 - ii. Approved for use in children 12 years and older
 - iii. Available as an oral prodrug
 - f. Amantadine and rimantidine
 - i. Only provides activity against influenza A
 - ii. Currently NOT recommended for treatment or prophylaxis because of resistance

- iii. U.S. Food and Drug Administration (FDA) label approved for treatment and prophylaxis for patients 1 year and older
5. Treatment considerations
 - a. Dosages must be adjusted in renal impairment.
 - b. If a commercially available suspension is not available, an extemporaneous suspension can be compounded from capsules (recipe provided by the manufacturer).
 - c. Cost

Table 1. Doses of Antiviral Agents Used for Influenza Treatment and Prophylaxis

Medication	Age		Treatment	Chemoprophylaxis
Oseltamivir	< 14 days		3 mg/kg/dose BID	Not recommended
	14 days – 2 mo		3 mg/kg/dose BID	Not recommended
	3–8 mo		3 mg/kg/dose BID	3 mg/kg/dose daily
	9–11 mo		3.5 mg/kg/dose BID	3.5 mg/kg/dose daily
	≥ 12 mo	≤ 15 kg	30 mg BID	30 mg daily
		> 15–23 kg	45 mg BID	45 mg daily
		> 23–40 kg	60 mg BID	60 mg daily
		> 40 kg	75 mg BID	75 mg daily
Zanamivir	< 5 yr		Not recommended	Not recommended
	5–6 yr		Not recommended	10 mg (2 inhalations) once daily
	≥ 7 yr		10 mg (2 inhalations) BID	10 mg (2 inhalations) once daily
Baloxavir marboxil	<12 yr weight-directed dose		2 mg/kg once (max 40 mg/dose)	< 10 kg: 1 mg/kg once
	<12 yr fixed dosing			< 10 kg: 1 mg/kg once
		5 to < 10 kg	Single dose of 5 mg	
		10 to < 20 kg	Single dose of 10 mg	Single dose of 10 mg
		20 to < 40 kg	Single dose of 20 mg	Single dose of 20 mg
		≥ 40 kg	Single dose of 40 mg	Single dose of 40 mg
	≥ 12 yr	< 80 kg	Single dose of 40 mg	Single dose of 40 mg
		≥ 80 kg	Single dose of 80 mg	Single dose of 80 mg
Peramivir	≥ 6 mo		12 mg/kg/dose IV as a single dose (max 600 mg/dose)	Not recommended
	Adolescents		600 mg IV as a single dose	Not recommended

BID = twice daily; IV = intravenous(ly).

B. Bronchiolitis

1. Most common viral lower respiratory tract infection in children younger than 2 years caused by acute inflammation, edema, and necrosis of the epithelial cells of the bronchioles
 - a. Increased mucus production
 - b. Bronchospasm
2. Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis.

3. Signs and symptoms
 - a. Cough
 - b. Wheeze
 - c. Rhinorrhea
 - d. Tachypnea
 - e. Grunting
 - f. Nasal flaring
 - g. Retractions
 - h. Fever
 - i. Decreased oral intake
 - j. Lethargy
4. Risk factors
 - a. Prematurity
 - b. Underlying cardiac or pulmonary disease
 - c. Immunodeficiency
 - d. History of wheezing
5. Treatment
 - a. Inhaled bronchodilators (albuterol, inhaled epinephrine) – No longer recommended by the American Academy of Pediatrics in infants 1–23 months presenting with RSV because of lack of benefit
 - b. Corticosteroids – Not recommended, given marginal benefit and lack of safety data
 - c. Antiviral therapy – Ribavirin; not recommended, given marginal benefit, high cost, and difficulty of administration. Must be administered by aerosol inhalation with specific small particle aerosol generator (which can lead to toxicity in any exposed health care personnel)
 - d. Supplemental O₂ – Indicated for patients with a peripheral capillary oxygen saturation less than 90% on room air
 - e. Hypertonic saline 3% solution – Not recommended for patients in the ED but may be used for inpatients with a length of stay greater than 72 hours
6. Prophylaxis
 - a. Palivizumab
 - i. Indicated for infants younger than 12 months at high risk of a serious lower respiratory tract infection caused by RSV. May be given up to 24 months in patients who require supplemental oxygen for at least 28 days after birth and continue to require medical intervention (corticosteroids, supplemental oxygen, diuretics) in the second year of life
 - ii. Given intramuscularly at a dose of 15 mg/kg for up to five monthly doses from November to March
 - iii. Monthly administration should be discontinued in infants who experience a breakthrough RSV hospitalization.
 - b. Palivizumab guidelines for administration published in July 2014 (reaffirmed in 2019)
 - i. Infants born before 29 weeks, 0 days' gestation and younger than 12 months at the start of RSV season
 - ii. Infants with chronic lung disease of prematurity defined as gestational age younger than 32 weeks, 0 days, and a requirement for O₂ (greater than 21%) for the first 28 days of life – Patients still requiring medical support (chronic corticosteroids, diuretics, supplemental O₂) for chronic lung disease during the second year of life may receive palivizumab prophylaxis.
 - iii. Infants 12 months and younger with hemodynamically significant congenital heart disease (and consultation with a pediatric cardiologist)
 - (a) Patients with acyanotic heart disease receiving medication for congestive heart failure and awaiting cardiac surgical procedures
 - (b) Moderate to severe pulmonary hypertension

- c. Nirsevimab
 - i. New single-dose monoclonal antibody for prevention of RSV infection
 - ii. Completed phase III trials for prevention of RSV in late-preterm and term infants (born at gestational age 35 weeks or greater)

II. UPPER RESPIRATORY TRACT INFECTIONS

A. Pharyngitis

1. Definition: Inflammation in the back of the throat between the tonsils and the larynx
2. Accounts for 10–15 million medical visits per year in the United States
3. Causes
 - a. Viral
 - i. Influenza A
 - ii. Enteroviruses (Coxsackievirus, echovirus)
 - iii. Rhinovirus
 - iv. Adenovirus
 - v. Parainfluenza
 - vi. Epstein-Barr virus – Cause of infectious mononucleosis, pharyngitis present in about 80% of patients
 - vii. Herpes simplex virus (HSV) 1 and 2
 - viii. Cytomegalovirus
 - b. Bacterial
 - i. Group A *Streptococcus* (GAS) (*Streptococcus pyogenes*) is the most common bacterial cause of acute pharyngitis, leading to 20%–30% of sore throat medical visits in children.
 - ii. *Neisseria gonorrhoeae*
 - iii. *Corynebacterium diphtheria*
 - iv. *Fusobacterium necrophorum*
 - v. *Mycoplasma pneumoniae*
 - vi. *Chlamydophila pneumoniae*
4. Clinical presentation and epidemiology
 - a. GAS
 - i. 5–15 years of age
 - ii. Occurs in winter or early spring
 - iii. Sudden onset
 - iv. Sore throat
 - v. Fever
 - vi. Headache
 - vii. Nausea, vomiting
 - viii. Inflammation of the tonsils
 - ix. Patchy exudate on tonsils or pharynx
 - b. Viral
 - i. Cough
 - ii. Hoarseness
 - iii. Conjunctivitis
 - iv. Diarrhea
 - v. Absence of fever

5. Diagnosis
 - a. Difficult to distinguish between viral and GAS pharyngitis
 - b. Swab of throat for rapid antigen detection test (RADT) and culture are indicated to determine the presence of GAS.
 - i. RADT tests are 95% specific, but have only a 70%–90% sensitivity.
 - ii. If RADT test negative, follow up with a throat culture. Throat culture is 90%–95% sensitive for GAS detection.
 - (a) Because of the risk of rheumatic fever
 - c. Rapid detection PCR-based assays are also available that provide higher sensitivity; however, they are also associated with a higher cost and are not as routinely available.
6. Treatment
 - a. Antimicrobial therapy indicated for GAS pharyngitis (in patients with a positive RADT and/or positive throat culture)
 - b. Patients without penicillin allergies
 - i. Penicillin VK orally for 10 days
 - (a) Children: 250 mg two or three times daily
 - (b) Adolescents: 250 mg four times daily or 500 mg twice daily
 - ii. Amoxicillin orally
 - (a) 50 mg/kg/dose once daily (maximum 1000 mg) or 25 mg/kg/dose (maximum 500 mg) twice daily for 10 days
 - iii. Benzathine penicillin G intramuscularly for one dose
 - (a) 600,000 international units if weight is less than 27 kg
 - (b) 1,200,000 international units if weight is 27 kg or more
 - c. Patients with a penicillin allergy AND no immediate type 1 hypersensitivity to penicillin
 - i. Cephalexin 20 mg/kg/dose twice daily (maximum 500 mg/dose) for 10 days
 - ii. Cefadroxil 30 mg/kg/dose once daily (maximum 1000 mg) for 10 days
 - d. Patients with a type 1 immediate (anaphylactic) hypersensitivity reaction to penicillin
 - i. Clindamycin 7 mg/kg/dose three times daily (maximum 300 mg/dose) for 10 days
 - ii. Azithromycin (5 days) or clarithromycin (10 days) may be used as an alternative; however, there is variable geographic resistance of GAS to these antibiotics.
 - e. Adjunctive agents are indicated for both viral and bacterial causes of pharyngitis (limited use, given risk).
 - i. Analgesic/antipyretic agents, acetaminophen or ibuprofen, can be used for moderate to severe symptoms or management of fever.
 - ii. Topical agents (rinses, sprays, lozenges) may also be used for relief of symptoms.
 - (a) Most agents contain topical anesthetics such as lidocaine or benzocaine.
 - (b) Lozenges can cause choking in smaller children.
 - (c) Limit use because of concern for systemic toxicity.
7. Complications of GAS pharyngitis
 - a. Nonsuppurative
 - i. Rheumatic heart disease
 - (a) Uncommon in developed countries
 - (b) Leading cause of acquired heart disease in India, sub-Saharan Africa, Australia, and New Zealand
 - (c) Prompt diagnosis and treatment of GAS pharyngitis can decrease the development of rheumatic heart disease.
 - ii. Poststreptococcal glomerulonephritis

- b. Suppurative
 - i. Otitis media
 - ii. Sinusitis
 - iii. Peritonsillar abscess
 - iv. Retropharyngeal abscess
 - v. Cervical lymphadenitis
 - vi. Mastoiditis
 8. Asymptomatic household contacts should not receive a throat culture or treatment.
- B. Laryngotracheitis (croup)
 1. Definition: Inflammation of the larynx and trachea (may also extend into the bronchi)
 2. Clinical presentation
 - a. Characterized by the presence of inspiratory stridor, a seal-like barking cough, and hoarseness; usually occurs in the early hours of the night
 - b. Most common in children younger than 3 years
 - c. Preceded by upper respiratory symptoms for 1–3 days
 - d. Often self-limiting and resolves in 3–5 days
 3. Cause: Parainfluenza virus types 1 and 2
 4. Diagnosis: Radiography of the neck. Anterior and posterior views of the soft tissue reveal a narrowing of the air column as a result of subglottic edema (“steep sign”).
 5. Treatment
 - a. Nonpharmacologic – Humidified O₂ in the presence of documented hypoxia (O₂ saturation less than 90%)
 - b. Pharmacologic
 - i. Racemic epinephrine (2.25% solution)
 - (a) Alpha effects reduce localized edema and decrease bronchial secretions.
 - (b) Beta effects lead to smooth muscle relaxation.
 - (c) Administered by nebulizer. 0.05–0.1 mL/kg (maximum dose 0.5 mL) diluted in 2 mL of normal saline
 - (d) A single dose is sufficient to relieve symptoms.
 - (1) Assess the need for additional doses (if patient still has stridor at rest after initial dose).
 - (2) Monitor for 3–4 hours after administration for the possibility of symptoms returning to baseline, “rebound phenomenon”
 - ii. Corticosteroids: Dexamethasone
 - (a) Used for moderate to severe episodes
 - (b) Improvement in respiratory status within 12–24 hours
 - (c) First line because of rapid onset, long half-life (usual duration of croup), and peak of action between 6 and 8 hours
 - (d) Dose: Single dose of 0.6 mg/kg/dose given orally, intramuscularly, or intravenously (maximum dose: 10–16 mg)
- C. Acute Rhinosinusitis
 1. Definition: Inflammation of the mucosal lining of the nasal passage and paranasal sinuses lasting for up to 1 month
 2. Causes
 - a. Viral (more than 90% of cases)
 - b. Bacterial (less than 10% of cases) – *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*

3. Criteria used to distinguish viral infection from bacterial infection
 - a. Persistent signs or symptoms for 10 days or more without clinical improvement
 - b. Severe signs or symptoms or temperature of 39°C or higher and purulent nasal discharge or facial pain for 3–4 consecutive days
 - c. Worsening signs or symptoms after a viral upper respiratory tract infection (“double sickening”)
 4. Treatment
 - a. Bacterial
 - i. High-dose amoxicillin/clavulanate (90 mg/kg/day divided twice daily) for 10–14 days (high dose required to overcome penicillin-nonsusceptible *S. pneumoniae* strains)
 - ii. Third-generation cephalosporin plus clindamycin – Used as an alternative in patients with non-type 1 hypersensitivity reactions to penicillin
 - iii. Levofloxacin for patients with type 1 hypersensitivity to penicillin
 - b. Adjunctive therapy
 - i. Intranasal corticosteroids are recommended, especially in patients with a history of allergic rhinitis.
 - ii. Topical or oral decongestants or antihistamines are NOT recommended for patients with sinusitis.
 - c. Nonpharmacologic – Nasal saline irrigation
- D. Epiglottitis
1. Definition: Inflammation of the epiglottis; considered a life-threatening airway emergency
 2. Causes
 - a. Bacterial
 - i. *H. influenzae* type b (Hib)
 - (a) Very rare because of universal Hib vaccination
 - (b) Can occur in unvaccinated or incompletely immunized children
 - ii. *S. aureus*
 - iii. *S. pneumoniae*
 - iv. *S. pyogenes*
 - v. *N. meningitidis*
 - vi. *Pasteurella multocida*
 - b. Immunocompromised patients are also at risk of *P. aeruginosa*, *Serratia*, *Enterobacter*, and anaerobes.
 - c. Can also occur because of direct injury of the epiglottis
 3. Clinical presentation
 - a. Symptoms develop rapidly over a few hours.
 - b. Fever, severe sore throat, drooling, stridor, dysphagia
 4. Treatment
 - a. Secure/maintain an open airway.
 - b. Third-generation cephalosporin (ceftriaxone) to target respiratory flora. Coverage to include activity against *S. aureus* may be considered. The antistaphylococcal agent can be determined by local methicillin-resistant *S. aureus* (MRSA) prevalence.
 - i. Antistaphylococcal antimicrobial options include vancomycin, clindamycin, nafcillin, oxacillin, or cefazolin.
 - ii. Vancomycin is recommended in patients with concomitant moderate or severe sepsis or meningitis.
 5. Prevention: Hib vaccination

III. ACUTE OTITIS MEDIA

- A. Definition: Acute onset of signs and symptoms, presence of middle ear effusion, and signs of middle ear inflammation. Distinguished from otitis media with effusion, which is defined as an accumulation of liquid in the middle ear cavity and the absence of signs and symptoms of acute infection
- B. Additional Definitions
 - 1. Uncomplicated acute otitis media (AOM): AOM without otorrhea
 - 2. Nonsevere AOM: AOM with mild otalgia plus temperature less than 39°C
 - 3. Severe AOM: AOM with severe otalgia plus temperature of 39°C or higher
 - 4. Recurrent AOM
 - a. Three or more episodes of AOM in past 6 months OR
 - b. Four or more episodes in the past 12 months (with one in the past 6 months)
- C. Epidemiology
 - 1. Most common diagnosis for which antimicrobial therapy is prescribed in infants and children
 - 2. 50% of the children in the United States will experience AOM by 6 months of age.
 - 3. Highest incidence at 3–24 months of age
- D. Risk Factors
 - 1. Day care attendance
 - 2. Lack of breastfeeding
 - 3. Presence of siblings
 - 4. Lower socioeconomic status
 - 5. Exposure to cigarette smoke
 - 6. Winter months
 - 7. Anatomic malformations (e.g., cleft palate, Down syndrome)
 - 8. White race
 - 9. First episode when younger than 6 months
- E. Causes
 - 1. Bacteria, viruses, polymicrobial (bacteria plus viruses)
 - 2. Bacteria are the most common cause of AOM in children (more than 60% of cases).
 - a. *S. pneumoniae* – 15%–25%
 - b. *H. influenzae* – 50%–60%
 - c. *M. catarrhalis* – 10%–15%
 - d. *S. pyogenes* is more common in older children and is associated with local complications such as mastoiditis.
 - 3. Viruses are not usually isolated, given lack of culturing with PCR.
 - a. Viral percentages vary.
 - b. Viral respiratory infections may predispose patients to AOM.
 - c. Common viral causes are RSV, rhinovirus, coronavirus, and parainfluenza virus.
 - 4. Bacterial resistance
 - a. Rates vary geographically
 - b. Penicillin intermediate and non-susceptible *S. pneumoniae* rates are increasing.
 - c. β -Lactamase production
 - i. *H. influenzae* – 35%–45%
 - ii. *M. catarrhalis* –100%

F. Signs and Symptoms (Table 2)

Table 2. Signs and Symptoms of Acute Otitis Media

Signs	Symptoms
Bulging tympanic membrane	Otalgia (pulling of ear in young children)
Middle ear effusion	Fever
Otorrhea	Irritability
Nonmobile tympanic membrane	Nasal stuffiness
Erythema of tympanic membrane	Changes in sleep/behavior
	Excessive crying
	Decreased appetite

G. Diagnosis

1. Signs and symptoms
2. Inspection of TM with a pneumatic otoscope
3. Tympanometry
4. Cultures (not routine)
5. Diagnostic criteria
 - a. Moderate to severe bulging of TM **OR** new onset of otorrhea
 - b. Mild bulging of the TM **AND** recent ear pain (for less than 48 hours) or intense erythema of TM
 - c. AOM should NOT be diagnosed without the presence of a middle ear effusion (by pneumatic otoscope).

Patient Case

1. A 3-year-old boy (weight 14 kg [30 lb]) presents to the clinic with irritability, a temperature of 38.5°C, and mild ear pain. On examination, his ear is erythematous with a copious amount of cerumen throughout the ear canal. He has had two previous episodes of AOM at 18 months and 2 years. He previously received amoxicillin; however, he developed a rash on his trunk after 5 days of therapy. According to the AOM guidelines, which therapy would be best for this patient?
 - A. Cefdinir 100 mg orally every 12 hours × 10 days.
 - B. Observation and pain management for 48–72 hours.
 - C. Azithromycin 150 mg orally × 1; then 75 mg orally once daily × 4 days.
 - D. Ceftriaxone 700 mg intramuscularly × 3 doses.

H. Treatment

1. Pain management
 - a. Mild pain
 - i. Acetaminophen 10–15 mg/kg/dose orally every 4–6 hours as needed (maximum dose 75 mg/kg/day)
 - ii. Ibuprofen 5–10 mg/kg/dose orally every 6 hours as needed in patients older than 6 months (maximum dose 40 mg/kg/day)
 - iii. Otological agents no longer recommended (benzocaine, antipyrine) or marketed because of lack of FDA approval
 - b. Moderate-severe pain: Narcotic analgesics are recommended.
2. Observation
 - a. Deferment of antibiotics for 48–72 hours

- b. Controlled trials have shown that 7–20 children must be treated for one child to benefit from antibiotic therapy.
- c. AOM resolves spontaneously in most patients.
- d. Decreases patient cost, resistance, and unwanted adverse effects
- e. Who should receive observation as an option?
 - i. Patients with nonsevere unilateral AOM (6–23 months) without severe symptoms
 - ii. Patients 24 months of age or older with AOM without severe symptoms
 - iii. Patients with a mechanism in place to ensure a follow-up at 48–72 hours
3. Antibiotic therapy (Table 3)
 - a. Recommended only in the following patients:
 - i. Younger than 6 months AND severe signs and symptoms OR temperature 39°C (102.2°F) or higher (severe signs and symptoms: moderate to severe otalgia or otalgia lasting for at least 48 hours)
 - ii. 6–24 months **AND** bilateral AOM without severe signs and symptoms

Table 3. Antimicrobial Therapy for Acute Otitis Media

Recommended First-line Treatment	Alternative Treatment (penicillin allergy)	Treatment After 48–72 Hr of Failure of Initial Treatment
High-dose amoxicillin (80–90 mg/kg/day orally divided BID-TID) OR High-dose amoxicillin/clavulanate ^a (90 mg/kg/day amoxicillin component orally divided BID)	Cefdinir (14 mg/kg/day orally divided once or twice daily) Cefuroxime (30 mg/kg/day orally divided BID) Cefpodoxime (10 mg/kg/day orally divided BID) Ceftriaxone (50 mg/kg (max 1000 mg) IM or IV once daily for 1–3 days)	Ceftriaxone 50 mg/kg (max 1000 mg) IV or IM once daily for 3 days Clindamycin (30–40 mg/kg/day orally divided TID) ± third-generation cephalosporin

^aHigh-dose amoxicillin/clavulanate is recommended first line in children treated with amoxicillin in the past 30 days OR concurrent purulent conjunctivitis OR history of recurrent AOM.

BID = twice daily; IM = intramuscular(ly); IV = intravenously; TID = three times daily.

- b. Duration of antibiotic therapy with β -lactams
 - i. Children younger than 2 years and children (of any age) with severe symptoms or a history of recurrent AOM: 10 days
 - ii. Children 2–5 years of age with mild to moderate symptoms: 7 days
 - iii. Children 6 years and older with mild to moderate symptoms: 5–7 days
 - iv. Patients who do not respond to initial therapy within 48–72 hours should be reassessed and changed to a different antibiotic.
4. Complications
 - a. Hearing loss
 - b. Perforation of TM
 - c. Otorrhea
 - d. Recurrent otitis media
 - e. Persistent middle ear effusion
 - f. Mastoiditis

5. Prevention of recurrent otitis media
 - a. Insertion of tympanostomy tubes
 - b. Vaccination
 - i. Pneumococcal conjugate vaccine (Prevnar)
 - ii. Influenza vaccine
 - iii. *Haemophilus influenzae* type b (Hib) conjugate vaccine
 - c. Modification of risk factors
6. Treatment of patients with tympanostomy tube placement and otorrhea
 - a. Topical antibiotic ear drops containing a fluoroquinolone plus a corticosteroid can be given if otorrhea does not resolve spontaneously in 1 week.

IV. SKIN AND SOFT TISSUE INFECTIONS

A. Purulent Skin and Soft Tissue Infections

1. Impetigo
 - a. Description
 - i. Superficial skin infection that can easily be transmitted from person to person
 - (a) Bullous
 - (b) Nonbullous
 - ii. Most common on face and in hot, humid weather
 - iii. Small, fluid-filled vesicles that develop into pus-filled blisters
 - iv. Blisters rupture to form golden-yellow crusts.
 - v. Pruritus is common.
 - vi. Systemic symptoms are rare.
 - b. Microorganisms
 - i. *Staphylococcus aureus* (80% of cases) or *S. pyogenes* (10% of cases) or coinfection with both organisms (10% of cases)
 - ii. Bullous impetigo caused by toxin produced by *S. aureus*. Isolation of MRSA is increasing (20% of cases).
 - c. Treatment
 - i. May resolve spontaneously
 - ii. Topical antibiotics can be considered for a mild clinical presentation.
 - (a) Limited lesions
 - (b) Area of infection does not include any mucosal areas
 - (c) Topical mupirocin or topical retapamulin 1% ointment
 - iii. Oral therapy is indicated for more extensive lesions or when topical therapy is impractical.
 - (a) Dicloxacillin (25–50 mg/kg per day in four divided doses) or cephalexin (25–50 mg/kg per day in three or four divided doses)
 - (b) Clindamycin (10 mg/kg/dose every 8 hours), doxycycline (2–4 mg/kg per day in two divided doses), or trimethoprim/sulfamethoxazole (8–12 mg/kg of trimethoprim per day in two divided doses) if MRSA is suspected (or in patients with a β -lactam allergy unable to tolerate cephalosporins)
2. Cutaneous abscesses, furuncles, carbuncles purulent
 - a. Description
 - i. Cutaneous abscess: Collection of pus within the dermis and deeper layers of the skin
 - ii. Furuncles/carbuncles: Boils or infections of the hair follicles
 - b. Microorganisms
 - i. *S. aureus* (including MRSA)

- c. Treatment
 - i. Mild infection: Treatment with incision and drainage is indicated.
 - ii. Moderate infection
 - (a) Purulent infection plus systemic signs and symptoms of infection
 - (b) Treatment
 - (1) Incision and drainage
 - (2) Culture and sensitivity
 - (3) Empiric (include coverage for MRSA until cultures return)
 - (A) Trimethoprim/sulfamethoxazole
 - (B) Doxycycline (in patients 8 years and older)
 - (C) Clindamycin (if local clindamycin resistance is less than 10%–15%)
 - (4) Defined
 - (A) MRSA: Trimethoprim/sulfamethoxazole
 - (B) Methicillin-sensitive *S. aureus* (MSSA): Dicloxacillin or cephalexin
 - iii. Severe infection
 - (a) Failure of incision and drainage and course of oral antibiotics OR systemic signs of infection (temperature higher than 38°C, heart rate greater than 90 beats/minute, respiratory rate greater than 24 breaths/minute, WBC greater than 12×10^3 cells/mm³ or less than 4×10^3 cells/mm³)
 - (b) Immunocompromised patients should be treated as having a severe infection.
 - (c) Treatment
 - (1) Incision and drainage
 - (2) Culture and sensitivity
 - (3) Empiric
 - (A) Vancomycin
 - (B) Clindamycin (if local clindamycin resistance less than 10%–15%)
 - (4) Defined
 - (A) MRSA: Vancomycin or clindamycin
 - (B) MSSA: Nafcillin/oxacillin, cefazolin
 - iv. Treatment duration
 - (a) Mild infection: 5 days
 - (b) Moderate or severe infection: Typically 10–14 days, depending on severity
- B. Nonpurulent Skin and Soft Tissue Infections
1. Cellulitis
 - a. Description
 - i. Acute, spreading infection of the skin with involvement of the deeper dermis and subcutaneous tissue
 - ii. Wound usually precedes infection.
 - iii. Edema, erythema, warm to touch
 - iv. Non-elevated lesions with poorly defined margins
 - v. May have involvement of lymph nodes
 - b. Microorganisms
 - i. *S. pyogenes* (70%–75% of cases)
 - ii. *S. aureus* (25%–30% of cases) (including MRSA)
 - iii. Uncommon causes: Anaerobes, gram-negative bacilli
 - c. Clinical presentation
 - i. Mild infection: Absence of systemic signs of infection
 - ii. Moderate infection: Systemic signs and symptoms of infection. Symptoms: Fever, chills, malaise

- iii. Severe infection
 - (a) Patients whose oral antibiotics have failed to work
 - (b) Patients with systemic signs of infection (as defined above for purulent infections)
 - (c) Immunocompromised patients
 - (d) Clinical signs of a deeper infection (bullae, skin sloughing, hypotension, organ dysfunction)
- d. Treatment
 - i. Mild infection (oral therapy)
 - (a) Penicillin VK
 - (b) Amoxicillin
 - (c) Dicloxacillin
 - (d) Cephalexin
 - (e) Clindamycin (reserved for patients with a β -lactam allergy unable to tolerate cephalosporins)
 - ii. Moderate infection (intravenous therapy)
 - (a) Penicillin G
 - (b) Cefazolin
 - (c) Ceftriaxone
 - (d) Clindamycin
 - iii. Severe infection
 - (a) Emergency surgical evaluation to rule out necrotizing infection
 - (b) Empiric: Vancomycin PLUS piperacillin/tazobactam
- e. Treatment duration
 - i. Mild infection: 5–10 days
 - ii. Moderate or severe infection: Typically 10–14 days, depending on severity

Patient Case

Questions 2 and 3 pertain to the following case.

T.P. is a 16-month-old boy (weight 12 kg) admitted to the hospital for a worsening abscess on his right lower inguinal area. The abscess, which appeared 3 days ago, was initially treated at the physician's office with incision and drainage. The area around the abscess is warm and erythematous. The patient has a temperature of 39.2°C, a WBC of 20×10^3 cells/mm³ (46% segs, 15% bands), and a C-reactive protein (CRP) of 12.8 mg/dL (normal is less than 0.1 mg/dL). The patient has also been receiving oral cephalexin for the past 48 hours. The wound culture from the physician's office is growing MRSA with the following sensitivities. Sensitive: Clindamycin (positive D-test), levofloxacin, linezolid, vancomycin, doxycycline, sulfamethoxazole/trimethoprim. Resistant: Erythromycin, oxacillin, tetracycline.

- 2. Which antibiotic would be best to initiate in the hospital, given these sensitivities?
 - A. Cefazolin 500 mg intravenously every 8 hours.
 - B. Clindamycin 120 mg intravenously every 8 hours.
 - C. Vancomycin 180 mg intravenously every 6 hours.
 - D. Linezolid 120 mg intravenously twice daily.
- 3. Which oral antibiotic therapy would you most likely recommend for T.P. on discharge?
 - A. Clindamycin 150 mg orally every 8 hours.
 - B. Doxycycline 24 mg orally every 12 hours.
 - C. Linezolid 120 mg orally twice daily.
 - D. Sulfamethoxazole/trimethoprim 60 mg orally every 12 hours.

2. Erysipelas
 - a. Description
 - i. Infection of superficial layers of skin and cutaneous lymphatics
 - ii. Sudden onset of fiery, red, painful plaque
 - iii. Clear margins, raised lesions
 - iv. Flu-like symptoms before lesion (contrast with clinical presentation of cellulitis)
 - v. Usually involves face or lower extremities
 - b. Microorganism: GAS (*S. pyogenes*)
 - c. Treatment: Penicillin, cephalexin, or clindamycin (for those with β -lactam allergies unable to tolerate cephalosporins) for 7–10 days
 3. Necrotizing fasciitis
 - a. Description
 - i. Rare, but severe
 - ii. Acute, necrotizing infection of subcutaneous tissue that leads to progressive destruction of superficial fascia and subcutaneous fat
 - iii. Firm on palpation
 - iv. Early onset of systemic toxicity, including septic shock
 - b. Microorganisms
 - i. Type I (polymicrobial)
 - (a) *Bacteroides* or *Peptostreptococcus* plus *Streptococcus* plus Enterobacterales
 - (b) Slow spreading
 - ii. Type II (*S. pyogenes*)
 - iii. Type III (*Clostridium perfringens*)
 - c. Treatment
 - i. Surgical debridement is first line.
 - ii. Antibiotic therapy
 - (a) Empiric therapy: Vancomycin PLUS piperacillin/tazobactam PLUS clindamycin
 - (b) Defined therapy
 - (1) Streptococcal or clostridial spp. – Penicillin G plus clindamycin (clindamycin added for suppression of toxins produced by organisms)
 - (2) Polymicrobial – As few agents as possible with coverage against all offending pathogens
- C. Preseptal and Orbital Cellulitis
1. Definitions and epidemiology
 - a. Preseptal cellulitis occurs in the soft tissue of the eye anterior to the orbital septum and has not penetrated the orbital septum.
 - b. Orbital cellulitis occurs in the soft tissue of the eye posterior to the orbital septum.
 - c. Both occur in young children (preseptal in those younger than 2 years; orbital in those 5–10 years of age) and affect males and females equally.
 2. Microorganisms
 - a. Historically caused by the same organisms as in respiratory and sinus infections (*H. influenzae* and *S. pneumoniae*). Immunization against these two organisms has decreased the incidence.
 - b. Preseptal cellulitis – *Staphylococcus* and *Streptococcus* spp.
 - c. Orbital cellulitis – *S. pneumoniae*, GAS, *S. aureus* (including MRSA), nontypeable *H. influenzae*, *M. catarrhalis*
 3. Clinical presentation
 - a. Ocular edema, erythema, warmth, tenderness
 - b. Fever

- c. Increased WBC and elevated CRP are more common in orbital cellulitis.
- d. Orbital cellulitis may present with chemosis, proptosis, impaired ocular movement
- 4. Treatment
 - a. If there is low suspicion of MRSA, initiate ampicillin/sulbactam monotherapy as a first-line empiric agent.
 - i. Ceftriaxone can be used for patients with a penicillin allergy.
 - b. Severe disease or risk factors present for MRSA
 - i. Vancomycin plus ceftriaxone plus metronidazole
 - ii. Clindamycin can be considered as an alternative to vancomycin depending on local susceptibility patterns.
 - c. Treatment duration
 - i. Preseptal: 7–10 days
 - ii. Orbital: 14 days

V. BONE AND JOINT INFECTIONS

A. Osteomyelitis

- 1. Definition
 - a. Infection of the bone from either a hematogenous spread or a contiguous focus (with or without vascular insufficiency)
 - b. Occurs in about 1 in 5000 children
 - c. Acute, but can progress to chronic osteomyelitis (presence of necrotic bone)
- 2. Disease-specific microorganisms (in addition to the most common organisms listed in Table 4)

Table 4. Microorganisms in Osteomyelitis Based on Age

Age	Organism
Neonate (< 1 mo)	<i>S. aureus</i> , GBS, <i>Escherichia coli</i> , <i>Candida</i>
1 mo – 5 yr	<i>S. aureus</i> , <i>S. pyogenes</i> , <i>S. pneumoniae</i> , <i>Kingella kingae</i>
> 5 yr	<i>S. aureus</i> , <i>S. pyogenes</i>

GBS = group B *Streptococcus*.

- a. Sick cell disease: *Salmonella*
- b. Presence of a foreign body: Coagulase-negative *Staphylococcus*
- c. Puncture wound of the foot: *Pseudomonas aeruginosa*
- d. HIV or cat exposure: *Bartonella henselae*
- e. Immunocompromised: Enterobacteriales or fungi
- f. Human or animal bites: Anaerobes, *Pasteurella multocida*, or *Eikenella corrodens*
- 3. Clinical presentation and diagnosis: Local signs and symptoms
 - a. Inflammation
 - b. Pain
 - c. Swelling
 - i. Pseudoparalysis occurs in neonates and young infants.
 - ii. Refusal to bear weight
 - d. Systemic symptoms
 - i. Fever
 - ii. Irritability

- iii. Lethargy
 - iv. Symptoms of upper respiratory tract infection usually precede infections caused by *Kingella kingae*.
 - e. Diagnostic criteria
 - i. Elevated WBC
 - ii. Increased inflammatory markers, erythrocyte sedimentation rate (ESR), and CRP
 - iii. Presence of bacteria from a blood culture (only 50% of cases are positive) or bone biopsy
 - f. Imaging procedures
 - i. Radiography – Usually read as normal in first 2–3 weeks of infection
 - ii. Computed tomography (CT) scan
 - iii. Magnetic resonance imaging (MRI): Preferred method of imaging because of its high sensitivity (97%) and specificity (about 90%)
 - iv. Radionuclide imaging (bone scan)
 - (a) Technetium-99m is a common radiopharmaceutical given intravenously.
 - (b) Radiography performed after administration detects an increased uptake of the radionuclide in areas of localized inflammation. 80%–100% sensitive, low specificity
 - (c) Positive emission tomography (PET)
4. Treatment (Table 5)

Table 5. Empiric Treatment of Acute Hematogenous Osteomyelitis in Infants, Children, and Adolescents

Local CA-MRSA resistance < 10% to 20%	Local CA-MRSA resistance 10%–20% and local clindamycin resistance < 10% to 20%	Local CA-MRSA resistance ≥ 10% and local clindamycin resistance > 10%
Nafcillin/oxacillin or cefazolin	Clindamycin	Vancomycin

- a. Empiric
 - i. Intravenous penicillinase-resistant penicillin (nafcillin or oxacillin) or intravenous first-generation cephalosporin (cefazolin)
 - (a) Provide coverage against MSSA
 - (b) Considered first-line empiric agents in patients older than 5 years with no risk factors
 - ii. Clindamycin – Allergy to penicillin or concern for CA-MRSA
 - iii. Vancomycin – Concern for MRSA or other resistant gram-positive organisms
 - iv. If *K. kingella* suspected, can add ceftriaxone, ampicillin, or β -lactam/ β -lactamase inhibitor combination
- b. Bacteria-specific
 - i. *Salmonella*
 - (a) Third-generation cephalosporin or ampicillin
 - (b) Ciprofloxacin may be used in patients with a penicillin allergy or as oral step-down therapy.
 - ii. *Pseudomonas* – Ceftazidime or cefepime plus aminoglycoside
 - iii. MRSA
 - (a) Vancomycin – empiric therapy:
 - (1) 60–80 mg/kg/day divided every 6 hours for children 3 months to less than 12 years of age and normal renal function
 - (2) 60–70 mg/kg/day divided every 6–8 hours for children 12 years and older and normal renal function
 - (3) Goal area under the curve (AUC) target of 400–600 mg·hour/L assuming a vancomycin minimum inhibitory concentration (MIC) of 1 mg/L or less for MRSA
 - (4) Maximum empiric daily dosing: 3600 mg/day

- (b) Intravenous clindamycin (40 mg/kg/day divided every 6–8 hours)
 - (1) Alternative to vancomycin if patient is stable and no bacteremia or intravascular infection is present
 - (2) Must determine there is no inducible resistance (negative D-test) before continued use in CA-MRSA osteomyelitis
 - (3) Oral step-down therapy
- (c) Daptomycin or intravenous linezolid may be considered as alternatives in patients who cannot tolerate vancomycin or clindamycin or if there is presence of vancomycin-intermediate or vancomycin-resistant MRSA
 - (1) Linezolid
 - (A) Infants and children younger than 12 years: 10 mg/kg/dose every 8 hours
 - (B) Children 12 years of age and adolescents: 10 mg/kg/dose every 12 hours (maximum dose: 600 mg)
 - (C) Not recommended for use beyond 28 days because of risk of long-term adverse effects
 - (2) Daptomycin 6–10 mg/kg/day once daily (children older than 1 year)
- c. Treatment duration
 - i. Acute hematogenous osteomyelitis should be treated for 3–4 weeks.
 - ii. Chronic osteomyelitis may need to be treated longer.

Patient Case

Questions 4 and 5 pertain to the following case.

M.L. is a 14-year-old male adolescent (weight 82 kg) who presents to the clinic today with right lower leg pain and swelling for the past week and new onset of fever and malaise during the past 3 days. He has had a difficult time walking during the past 2 days. On examination, there is diffuse tenderness of the affected area secondary to the pain. The patient has no significant past medical problems but had a skateboarding accident 7 days ago. Laboratory results show the following: WBC 18×10^3 cells/mm³ (65% segs, 10% bands, 28% lymphs, 2% monos), ESR 52 mm/hour, and CRP 12.7 mg/dL. An MRI reveals soft tissue swelling of the right tibia and periosteum suggestive of osteomyelitis. M.L. is to be admitted to the hospital for intravenous antibiotic treatment. The local prevalence of CA-MRSA is less than 10%.

4. Which is the best empiric therapy for M.L.?
 - A. Ceftriaxone 1000 mg intravenously every 12 hours.
 - B. Ciprofloxacin 400 mg intravenously every 12 hours.
 - C. Cefazolin 1000 mg intravenously every 8 hours.
 - D. Clindamycin 600 mg intravenously every 6 hours.
5. On day 2 of hospitalization, a blood culture comes back positive for MSSA. The patient is hospitalized for 7 days to receive intravenous antibiotics. Which would be most appropriate for oral therapy, which will continue for another 3–4 weeks?
 - A. No appropriate oral agent for the organism.
 - B. Cephalexin 500 mg orally every 6 hours.
 - C. Ciprofloxacin 500 mg orally twice daily.
 - D. Linezolid 600 mg orally twice daily.

- d. Role of oral antimicrobial therapy
 - i. Oral antibiotics can be used to complete the 4- to 6-week treatment when clinical markers begin to normalize (afebrile, improved physical examination, decreasing ESR or CRP)
 - ii. No clear consensus on number of days of intravenous therapy required before transition to oral therapy
 - (a) Positive clinical outcomes have been shown in patients receiving as few as 2–4 days of intravenous therapy.
 - (b) Most experts recommend at least 1 week of intravenous therapy before oral therapy is initiated.
 - (c) For patients with negative blood cultures, the transition to oral therapy is associated with decreased length of hospital stay, decreased health care costs, and decreased risk of nosocomial infection.
 - iii. MSSA – Dicloxacillin or cephalexin
 - iv. MRSA – Clindamycin, linezolid, trimethoprim/sulfamethoxazole plus rifampin
 - e. Nonpharmacologic therapy
 - i. Surgical debridement – Recommended first line in combination with systemic antibiotics
 - ii. Hyperbaric O₂ therapy
 - (a) Chronic osteomyelitis
 - (b) Limited clinical experience in pediatric patients
- B. Infectious Arthritis
1. Definition and epidemiology
 - a. Infection of a monoarticular joint or joint space
 - b. More common in pediatric patients than osteomyelitis
 - i. 5–15 cases per 100,000 children
 - ii. Incidence varies among age groups; highest incidence occurs in those younger than 3 years and adolescents.
 - c. Hematogenous spread is the most common cause.
 2. Microorganisms (Table 6)

Table 6. Microorganisms Based on Age in Infectious Arthritis

Age	Organism
Neonates and infants < 2 mo	GBS, <i>E. coli</i> , <i>S. aureus</i>
2 mo – 5 yr	<i>S. aureus</i> , <i>S. pneumoniae</i> , <i>S. pyogenes</i> , <i>K. kingae</i>
> 5 yr	<i>S. aureus</i> , <i>S. pyogenes</i>
Adolescents	<i>S. aureus</i> , <i>N. gonorrhoeae</i>

3. Clinical presentation and diagnosis – Signs and symptoms
 - a. Acute systemic infection (fever, chills, malaise)
 - b. Acute onset of pain, tenderness, swelling of monoarticular joint
 - c. Markedly decreased range of motion
 - d. Common joints involved are knee and hip.

4. Diagnostic criteria
 - a. Laboratory data
 - i. Isolation of bacteria from a blood culture (50% of patients) or synovial fluid
 - ii. Leukocytosis of synovial fluid
 - iii. Decreased glucose in synovial fluid
 - iv. Increased lactate dehydrogenase, protein, and lactic acid in synovial fluid
 - v. Increased inflammatory markers (ESR, CRP)
 - b. Procedures
 - i. Aspiration of joint fluid
 - ii. Radionuclide imaging
 - iii. CT
 - iv. MRI
5. Pharmacologic therapy
 - a. Duration of antibiotic therapy is 3–4 weeks.
 - b. First-line empiric agents are the same as for osteomyelitis except as noted:
 - i. Sexually active adolescents – Ceftriaxone (plus staphylococcal coverage empirically)
 - ii. If *K. kingae* is suspected (younger than 5 years, upper respiratory tract infection symptoms):
Cephalosporin (i.e., ceftriaxone) plus staphylococcal coverage
6. Nonpharmacologic therapy
 - a. Joint aspiration: First-line treatment in combination with systemic antibiotics
 - b. Surgical debridement
 - c. Joint rest

VI. CENTRAL NERVOUS SYSTEM INFECTIONS

- A. Meningitis
 1. Introduction
 - a. Infection of the meninges and the CSF
 - b. More than 1 million cases reported annually worldwide
 - c. Mortality of 2%–30% in treated cases (mortality almost 100% if untreated)
 - d. 30%–50% risk of neurologic sequelae (e.g., seizures, hearing loss, impaired mental status)
 2. Microbiology
 - a. Bacterial
 - i. Increasing incidence in recent years of penicillin-resistant *S. pneumoniae*
 - ii. Decreasing incidence of *H. influenzae* because of worldwide Hib vaccination
 - b. Causes of aseptic meningitis (defined as inflammation of the meninges without a bacterial source) (Table 7)
 - i. Viruses (particularly HSV and enterovirus)
 - ii. Fungi
 - iii. *Cryptococcus neoformans*
 - iv. Parasites
 - v. Tuberculosis (TB)

Table 7. Most Common Causative Organisms by Age

Age Group	Organism
Neonate	GBS <i>E. coli</i> <i>Listeria monocytogenes</i>
1–23 mo	<i>S. pneumoniae</i> <i>N. meningitidis</i> <i>H. influenzae</i> (type B)
2–50 yr	<i>N. meningitidis</i> <i>S. pneumoniae</i>

3. Risk factors
 - a. Extremes of age
 - b. Exposure to cigarette smoke
 - c. Upper and lower respiratory infections
 - d. Neurosurgical procedures
 - e. Head trauma
 - f. Asplenia
 - g. Immunocompromised
4. Clinical presentation
 - a. Symptoms
 - i. Fever
 - ii. Headache, seizure, confusion, lethargy
 - iii. Vomiting
 - iv. Myalgia
 - v. Photophobia
 - vi. Nuchal rigidity
 - vii. Petechiae/purpura (most commonly associated with *Neisseria meningitidis*)
 - b. Signs
 - i. Brudzinski neck sign (may be absent in children). When the neck is flexed, the patient's hips and knees flex secondary to neck stiffness.
 - ii. Kernig sign (may be absent in children). Inability to straighten the leg when the hip is flexed to 90 degrees
 - iii. Bulging fontanelle (neonates and infants)
 - c. Diagnosis
 - i. History and physical examination
 - ii. Lumbar puncture (Table 8)
 - (a) CSF Gram stain and culture
 - (b) HSV polymerase chain reaction (PCR)
 - (c) Acid-fast staining (TB)
 - (d) India ink test (*Cryptococcus*)
 - (e) Cryptococcal antigen
 - iii. Blood culture
 - iv. CT
 - v. Rapid diagnostic panel now available to test CSF for common bacteria, viruses, and fungal causes of CNS infections

Table 8. CSF Findings in Meningitis

CSF Finding	Normal	Bacterial Meningitis	Aseptic Meningitis
Opening pressure	< 20 cm H ₂ O	Elevated	Normal
WBC (cells/mm ³)	< 5 (< 30 newborns)	↑ (1000–5000) neutrophil predominance	↑ (5–500) lymphocyte predominance
Glucose (mg/dL)	45–80	↓ (< 45)	Normal
CSF/serum glucose ratio	60%	< 30%	Normal
Protein	< 50 mg/dL	↑	Normal or increased

5. Empiric treatment (Table 9)

Table 9. Initial Empiric Therapy Based on Age Group

Age Group	Organism	Empiric Therapy
Neonate	GBS <i>E. coli</i> <i>L. monocytogenes</i>	Ampicillin + aminoglycoside ± extended-spectrum cephalosporin (ceftazidime, cefepime) (+ acyclovir if high suspicion of viral infection such as seizures at presentation, mucocutaneous vesicles, elevated liver enzymes, CSF pleocytosis)
1–23 mo	<i>S. pneumoniae</i> <i>N. meningitidis</i> <i>H. influenzae</i>	Vancomycin + ceftriaxone
2–50 yr	<i>N. meningitidis</i> <i>S. pneumoniae</i>	Vancomycin + ceftriaxone

6. Directed antibiotic therapy

- a. *S. pneumoniae* (duration 10–14 days)
 - i. Penicillin-susceptible isolates (MIC 0.06 mcg/mL or less): Penicillin G or ceftriaxone
 - ii. Penicillin-nonsusceptible isolates (MIC greater than 0.06 mcg/mL)
 - (a) Ceftriaxone MIC 0.5 mcg/mL or less: Ceftriaxone
 - (b) Ceftriaxone MIC 1 mcg/mL or greater: Vancomycin plus ceftriaxone plus rifampin
 - (c) Ceftriaxone MIC greater than 1 mcg/mL: Vancomycin plus ceftriaxone plus rifampin
 - b. *N. meningitidis*: Ceftriaxone (duration 7–10 days)
 - c. *H. influenzae*: Ceftriaxone (duration 7–10 days)
 - d. *L. monocytogenes*: Ampicillin with or without aminoglycoside (duration 21 days or more)
 - e. Group B *Streptococcus*: Penicillin G (duration 14–21 days)
 - i. Ampicillin may be considered as an alternative.
 - f. *E. coli*: Ceftriaxone (duration 21 days)
7. Alternative antibiotic therapy for patients with β-lactam allergies
 - a. Meropenem if non-life-threatening allergy
 - b. Aztreonam if life-threatening allergy

Patient Case

Questions 6 and 7 pertain to the following case.

P.E. is a 16-year-old male adolescent admitted to the hospital with fever, neck stiffness, and new-onset petechiae. His lumbar puncture in the ED reveals the following: CSF cloudy, WBC 2.5×10^3 cells/mm³ (80% segs, 10% bands, 10% lymphs), glucose 38 mg/dL, and protein 130 mg/dL. He is initially placed on empiric therapy with vancomycin plus ceftriaxone. Two days after admission, the CSF results show the presence of *N. meningitidis*.

6. Which changes would be best to P.E.'s antibiotic regimen, given these culture results?
 - A. Continue vancomycin and ceftriaxone.
 - B. Discontinue vancomycin and continue ceftriaxone.
 - C. Discontinue vancomycin, continue ceftriaxone, and add rifampin.
 - D. Change ceftriaxone and vancomycin to penicillin and rifampin.
7. Which would be best to initiate for P.E.'s household contacts?
 - A. Ceftriaxone 1 g intramuscularly every 24 hours $\times$ 7 days.
 - B. No chemoprophylaxis warranted for this pathogen.
 - C. Quadrivalent meningococcal conjugate vaccine intramuscularly $\times$ 1 dose.
 - D. Rifampin 600 mg orally every 12 hours $\times$ 2 days.
8. Chemoprophylaxis
 - a. Required for individuals in close contact with patients who have *N. meningitidis* or Hib (rifampin only)
 - b. Initiate in close contacts within 5–7 days after the patient's symptoms begin.
 - c. Agents
 - i. *N. meningitidis*
 - (a) Rifampin
 - (1) Neonates: 5 mg/kg orally every 12 hours for 2 days
 - (2) Infants, children, and adolescents: 15–20 mg/kg orally every 12 hours for 2 days (maximum 600 mg/dose)
 - (b) Ciprofloxacin: 1 month and older: 20 mg/kg orally once (maximum 500 mg)
 - (c) Ceftriaxone
 - (1) Younger than 15 years: 125 mg intramuscularly once
 - (2) 15 years and older: 250 mg intramuscularly once
 - ii. *H. influenzae*
 - (a) Rifampin: Only required in close contacts of patients who are not fully vaccinated against Hib or who are immunocompromised
 - (1) Neonates: 10 mg/kg orally once daily for 4 days
 - (2) Infants, children, and adolescents: 20 mg/kg orally once daily for 4 days (maximum 600 mg/dose)
9. Preventive strategies
 - a. Hib vaccine
 - b. 13-valent pneumococcal conjugate vaccine
 - c. Meningococcal conjugate vaccine – *N. meningitidis* serotypes A, C, Y, and W-135
10. Dexamethasone
 - a. May be used as adjunctive therapy given 10–20 minutes before first dose of antibiotics
 - i. 0.15 mg/kg/dose intravenously every 6 hours for 2–4 days
 - ii. Should not be initiated if antibiotics have already been administered

- b. Has been shown to decrease hearing loss in patients with *H. influenzae* meningitis (but not pneumococcal meningitis)
 - c. Controversial because has not been shown to decrease mortality or severe neurological sequelae
 - d. Can be discontinued when pathogen is isolated if it is not *H. influenzae*
- B. Central Nervous System (CSF) Shunt Infections
 - 1. Definition: Infection of a ventriculoperitoneal shunt
 - 2. Microorganisms – Coagulase-negative staphylococci, *S. aureus*, aerobic gram-negative bacilli, *Propionibacterium acnes*
 - 3. Treatment
 - a. Empiric systemic antimicrobial therapy
 - i. Vancomycin plus an antipseudomonal β -lactam (cefepime, ceftazidime, meropenem)
 - ii. Patients with type I hypersensitivity reactions (anaphylaxis) to β -lactams should receive aztreonam or ciprofloxacin for gram-negative coverage.
 - b. Intraventricular antibiotic instillation (no studies have defined the exact dose required for ventriculitis)
 - i. Vancomycin 5–20 mg daily
 - ii. Gentamicin 1–2 mg daily
 - iii. Tobramycin 5–20 mg daily
 - iv. Amikacin 5–30 mg daily
 - c. Removal of infected shunt and external drainage
- C. Health Care–Associated CNS Infections
 - 1. CSF shunt infection: Infection of a ventriculoperitoneal shunt
 - a. Microorganisms – Coagulase-negative staphylococci, *S. aureus*, aerobic gram-negative bacilli, *Propionibacterium acnes*
 - 2. Ventriculitis: Infection of the ventricles of the brain
 - a. Complication of meningitis (particularly in neonates)
 - b. Commonly associated with the presence of a CSF shunt or external ventricular drain
 - c. Microorganisms – Coagulase-negative staphylococci, *S. aureus*, aerobic gram-negative bacilli (*E. coli*, *Klebsiella* spp., *Acinetobacter*, *Pseudomonas*)
 - 3. Treatment
 - a. Empiric systemic antimicrobial therapy
 - i. Vancomycin plus an antipseudomonal β -lactam (cefepime, ceftazidime, meropenem)
 - ii. Patients with type I hypersensitivity reactions (anaphylaxis) to β -lactams should receive aztreonam or ciprofloxacin for gram-negative coverage.
 - b. Intraventricular antibiotic instillation (no studies have defined the exact dose required for ventriculitis)
 - i. Vancomycin 5–20 mg daily
 - ii. Gentamicin 1–2 mg daily
 - iii. Tobramycin 5–20 mg daily
 - iv. Amikacin 5–30 mg daily
 - c. Removal of infected shunt and external drainage

VII. URINARY TRACT INFECTIONS

A. Epidemiology

1. UTI prevalence from 2 months to 2 years of age is 7% (females/males is about 2:1).
2. Febrile UTIs have highest incidence in first year of life. Presence of fever increases the possibility of kidney involvement.
3. Acute pyelonephritis is the most common serious bacterial infection in childhood (13,000 hospital admissions per year). Defined as inflammation of renal parenchyma

B. Risk Factors

1. Girls
 - a. White race
 - b. Age younger than 12 months
 - c. Temperature 39°C or higher
 - d. Fever for 2 days or more
 - e. Absence of another source of infection
2. Boys
 - a. Black race
 - b. Uncircumcised
 - c. Temperature 39°C or higher
 - d. Fever for less than 24 hours
 - e. Absence of another source of infection

C. Pathogens

1. Bacterial infection of the mucosal surface of the urinary tract
 - a. *E. coli* (70%)
 - b. *Klebsiella pneumoniae*
 - c. Group B *Streptococcus* (neonates)
 - d. *Staphylococcus saprophyticus* (sexually active adolescents)
 - e. *Proteus mirabilis*
 - f. Other uncommon bacterial causes
 - i. *P. aeruginosa* (patients with complicated urogenital anatomy or presence of a urinary catheter)
 - ii. *Enterococcus faecalis*
 - iii. *S. aureus* or coagulase-negative *Staphylococcus*
2. Viral (adenovirus, BK virus)
3. Fungal (*Candida albicans*)

D. Clinical Presentation

1. Asymptomatic bacteriuria – Positive bacterial count on urine culture with no signs or symptoms
2. UTI
 - a. 3 months or younger: Temperature of 38°C or higher, hypothermia, vomiting, diarrhea, jaundice, irritability, decreased oral intake
 - b. 3–24 months of age: Cloudy or malodorous urine, increased frequency, hematuria, temperature of 38°C or higher
 - c. 2–6 years of age: Patients can verbalize symptoms.
3. Acute pyelonephritis
 - a. Fever (temperature higher than 39°C)
 - b. Abdominal or flank pain
 - c. Systemic symptoms (vomiting)

E. Diagnosis

1. Urine culture
 - a. Suprapubic aspiration or urethral catheterization is preferred to urine bag collection (“clean catch”).
 - b. Diagnostic criteria
 - i. Urethral catheterization: 50,000 CFU/mL
 - ii. Clean catch: Greater than 10^5 CFU/mL of one-pathogen colonies
2. Urinalysis – Detection of any of the following:
 - a. Nitrites
 - i. Highly specific for the presence of gram-negative bacilli
 - ii. Low sensitivity; negative values do not rule out UTI
 - b. Leukocyte esterase
 - i. Highly sensitive, but low specificity
 - ii. Can help distinguish patients with asymptomatic bacteruria
 - c. Pyuria (defined as 10 WBC/mm³ or more on an enhanced urinalysis, 5 WBC/mm³ or more per high power field, or presence of leukocyte esterase on a urine dipstick)
 - d. Bacteria
 - e. Red blood cells

F. Complications

1. Pyelonephritis
2. Renal scarring – Risk increases with recurrent UTIs.
 - a. Can lead to decreased kidney function and possible progression to chronic kidney disease
3. Vesicoureteral reflux (VUR)
 - a. Found in one-third of children with febrile UTIs
 - b. Risk of renal scarring
4. Progression of chronic kidney disease with recurrent UTIs

Patient Case

Questions 8 and 9 pertain to the following case.

D.M. is a 14-month-old girl (weight 10 kg) who presents to the physician’s office with reports that she has been fussy, with rectal temperatures of 39.8°C for 2 days. Her medical history is unremarkable, and her immunizations are up to date. She has had a decreased appetite for the past 24 hours but has had no nausea or vomiting. On examination, she appears well, with no apparent source of the fever. A urinalysis (bag collection) reveals the presence of leukocyte esterase, trace blood, WBC, and moderate bacteria. Nitrites are negative.

8. Which is the best empiric therapy for D.M.?
- A. Ciprofloxacin 150 mg orally every 12 hours.
 - B. Nitrofurantoin 20 mg orally every 24 hours.
 - C. Sulfamethoxazole/trimethoprim 40 mg of trimethoprim orally every 12 hours.
 - D. Amoxicillin 450 mg orally every 12 hours.

Patient Case (continued)

9. D.M. received a prescription for an oral antibiotic that she has been taking for 3 days. She returns to the clinic today with continued fever and new onset of nausea and vomiting and severe lower back pain. She is to be admitted to the hospital for treatment of presumed pyelonephritis. Which is most appropriate intravenous therapy to initiate at this time?
- A. Ciprofloxacin 30 mg/kg/day divided twice daily.
 - B. Ceftriaxone 50 mg/kg/day once daily.
 - C. Ampicillin 50 mg/kg/dose every 6 hours plus gentamicin 2.5 mg/kg IV q8hr.
 - D. Piperacillin/tazobactam 300 mg piperacillin/kg/day divided every 6 hours.

G. Treatment (Table 10)

1. Infants younger than 2 months: Hospitalize and give intravenous antibiotics.
2. Cystitis: Oral or intravenous antibiotics are equally efficacious, and treatment should be for 7–14 days.
3. Acute pyelonephritis
 - a. Oral or intravenous antibiotics for 10–14 days, depending on age and severity of symptoms
 - b. Hospitalize if dehydrated, ill-appearing, underlying chronic illness

Table 10. Empiric Antibiotic Treatment of Febrile UTIs

Treatment	Dose	Comments
Intravenous		
Ampicillin + gentamicin	Dose based on gestational age	First line therapy for neonates
Ceftriaxone	50 mg/kg/dose q24hr	Once daily, contraindicated < 4 wk of age
Gentamicin	5 mg/kg/dose q24hr	Once-daily dosing (alternatively, can use conventional dosing 2–2.5 mg/kg/dose q8hr)
Oral		
Sulfamethoxazole/trimethoprim	Age 2–24 mo: 3–6 mg/kg/dose trimethoprim q12hr Age > 24 mo: 4 mg/kg/dose trimethoprim q12hr	Geographic variation of resistance, contraindicated < 8 wk of age, risk of Stevens-Johnson syndrome
Amoxicillin/clavulanic acid	7–14 mg/kg/dose q8hr	Increasing resistance rates
Cefixime	8 mg/kg/dose q24hr	Once daily
Cephalexin	12.5–25 mg/kg/dose q6–8hr	Geographic variation of resistance
Cefpodoxime	Infants and children < 12 yr: 4–5 mg/kg/dose q12hr Children and adolescents ≥ 12 yr: 100–200 mg/dose q12hr	Alternatives to amoxicillin/clavulanate in patients with penicillin allergy
Cefprozil	15 mg/kg/dose q12hr	
Cefuroxime axetil	10–15 mg/kg/dose q12hr	
Ciprofloxacin	10–20 mg/kg/dose q12hr	Oral agent for coverage against <i>Pseudomonas</i> , second-line agent for complicated UTIs
Nitrofurantoin	1–2 mg/kg/dose q6hr	Not recommended for empiric treatment of febrile infants because it does not achieve therapeutic concentrations in the blood

UTI = urinary tract infection.

H. Evaluation

1. Febrile infants 2–24 months of age with a UTI should have a renal and bladder ultrasonography (RBUS) to determine the presence of anatomic abnormalities (e.g., hydronephrosis) or renal scarring. Recommended during first 2 days of treatment if no clinical improvement
2. Vesicoureteral voiding cystography is not recommended after the first UTI (unless abnormal RBUS).
 - a. Should be performed after recurrence of febrile UTI
 - b. Detects presence of VUR

I. Antimicrobial Prophylaxis

1. 2011 American Academy of Pediatrics guidelines recommend against the routine use of antimicrobial prophylaxis.
2. 2014 Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study showed a 50% reduction in recurrence of UTIs but no difference in renal scarring for patients with VUR.
3. Length of prophylaxis is typically 6 months (long-term prophylaxis may be needed in patients with more severe VUR).
4. Preferred agents if prophylaxis is indicated/initiated
 - a. Sulfamethoxazole/trimethoprim 2 mg/kg/dose once daily (for patients older than 8 weeks)
 - b. Amoxicillin 20–30 mg/kg/day divided twice daily (if younger than 8 weeks)
 - c. Nitrofurantoin 1–2 mg/kg/dose once daily (not recommended if severe renal impairment)
 - d. Cephalexin 12–15 mg/kg/dose once daily

VIII. CATHETER-RELATED BLOODSTREAM INFECTIONS**A. Epidemiology**

1. 1 of every 20 central venous catheters inserted results in one systemic infection.
2. 35,000 cases per year in the United States

B. Microorganisms

1. Coagulase-negative staphylococci – About 35% of cases and more than 50% of cases in neonates
2. *S. aureus* – Catheter-related bloodstream infections that involve normal skin flora occur more commonly with short-term vascular devices (less than 10 days).
3. Enteric gram-negative bacilli
4. *P. aeruginosa*
5. *Candida* spp. – Second most common cause in neonates

C. Risk Factors

1. Premature neonates
2. Hemodialysis
3. Parenteral nutrition
4. Chemotherapy
5. Immunosuppression
6. Short gut syndrome
7. Prolonged use of broad-spectrum antibiotics

D. Treatment (Table 11)

1. Removal of the central venous catheter is indicated for most infections.
 - a. Complicated – Presence of suppurative thrombophlebitis, osteomyelitis, endocarditis, possible metastatic seeding

- b. Uncomplicated
 - i. Resolution of fever and negative culture within 72 hours
 - ii. For *S. aureus* infections, no active malignancy or immunosuppression
- c. Removal of the catheter can pose a challenge in pediatric patients because of limited intravenous access.
2. Systemic antibiotic therapy – Day 1 of therapy is the first day of a negative blood culture.
3. Role of antibiotic lock therapy
 - a. Concept developed in 1980s to sterilize the catheter
 - b. Salvage therapy for patients with long-term central venous catheters when there is no option to remove the catheter
 - c. Provides supratherapeutic concentrations directly at the site of infection/colonizations
 - d. Can be used for both treatment and prevention
 - e. Treatment
 - i. Used in conjunction with systemic antimicrobial therapy
 - ii. Not indicated for *S. aureus* or *Candida* infections
 - iii. Agents used in antibiotic lock solutions
 - (a) Vancomycin
 - (b) Ceftazidime
 - (c) Cefazolin
 - (d) Ciprofloxacin
 - (e) Gentamicin
 - (f) Antifungals
 - (g) Ethanol

Table 11. Treatment of Intravascular Catheter-Related Infections

Type of CVC	Short Term (in place < 14 days)		Long Term (in place ≥ 14 days)	
Type of Infection	Complicated	Uncomplicated	Complicated	Uncomplicated
Recommendation	Remove catheter + systemic antibiotics for 4–6 wk	Coagulase-negative <i>Staphylococcus</i> Remove catheter + systemic antibiotics × 5–7 days If retained, systemic antibiotic + antibiotic lock × 10–14 days	Tunnel infection or port abscess Remove catheter + systemic antibiotics for 7–10 days	Coagulase-negative <i>Staphylococcus</i> Retained catheter, systemic antibiotic + antibiotic lock × 10–14 days
		<i>S. aureus</i> Remove catheter + systemic antibiotics for ≥ 14 days	Septic thrombosis, endocarditis, osteomyelitis Remove catheter + systemic antibiotics for 4–6 wk	<i>S. aureus</i> Remove catheter + systemic antibiotics for 4–6 wk
		<i>Enterococcus</i> Remove catheter + systemic antibiotics for 7–14 days		<i>Enterococcus</i> Retained catheter, systemic antibiotic + antibiotic lock × 7–14 days

Table 11. Treatment of Intravascular Catheter-Related Infections (*continued*)

Type of CVC	Short Term (in place < 14 days)		Long Term (in place ≥ 14 days)	
Type of Infection	Complicated	Uncomplicated	Complicated	Uncomplicated
		Gram-negative bacilli Remove catheter + systemic antibiotics for 7–14 days		Gram-negative bacilli Remove catheter + systemic antibiotics for 7–14 days Retained catheter, systemic antibiotic + antibiotic lock × 10–14 days
		<i>Candida</i> spp. Remove catheter + systemic antifungal for 14 days after first negative blood culture		<i>Candida</i> spp. Remove catheter/port + systemic antifungal for 14 days after first negative blood culture

CVC = central venous catheter.

E. Prevention

1. Strict adherence to sterile technique
2. Chlorhexidine or povidone-iodine cleaning solutions with catheter care
3. Topical antibiotic ointments applied around exit site
4. Antibiotic lock therapy

F. Role of Antibiotic Lock Therapy

1. Concept developed in 1980s to sterilize the catheter
2. Salvage therapy for patients with long-term central venous catheters when there is no option to remove the catheter
3. Provides supratherapeutic concentrations directly at the site of infection/colonizations
4. Can be used for both treatment and prevention

IX. ENDOCARDITIS

- A. Epidemiology – Less common infection in children than in adults; annual incidence rate in the United States is 1 in 1000–2000 pediatric admissions

B. Risk Factors

1. Congenital heart disease
2. Presence of central indwelling venous catheters

C. Diagnosis

1. Duke clinical criteria (major and minor criteria used to diagnose infective endocarditis)
 - a. Major criteria: Positive blood culture with typical microorganism or evidence of endocarditis on echocardiogram
 - i. Blood culture
 - ii. Echocardiography
 - b. Minor criteria: Temperature greater than 38°C, predisposing risk factors, embolism, immunological findings
2. Blood culture
3. Echocardiography

D. Clinical Presentation

1. Prolonged low-grade fever
2. Fatigue, weakness, myalgia
3. Weight loss
4. Presence of septic emboli
5. Neonates often present with heart murmur, respiratory distress, tachycardia, neurologic symptoms (seizure, apnea)

E. Microbiology

1. Viridans streptococci (20%–40%)
2. *S. aureus* (30%–50%)
3. Coagulase-negative staphylococci
4. *S. pneumoniae*
5. *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella* (HACEK) organisms
6. *Enterococcus*
7. Culture negative
8. *Candida* (neonates)

F. Treatment (Table 12)

1. Systemic antimicrobial therapy for 2–8 weeks

Table 12. Antimicrobial Treatment of Endocarditis

Organism	Antimicrobial Therapy	Alternative Therapy	Duration (wk)
Streptococci highly susceptible to penicillin (MBC $\leq$ 0.1 mcg/mL): • Viridans streptococci groups A, B, C, G • <i>S. bovis</i> , <i>S. equinus</i>	Penicillin G OR Ceftriaxone	Vancomycin OR Cefazolin	4
Streptococci relatively resistant to penicillin (MBC $\geq$ 0.2 mcg/mL), enterococci	Penicillin G + gentamicin OR Ampicillin + gentamicin (use if penicillin G is unavailable)	Ceftriaxone + gentamicin (streptococci only) Vancomycin + gentamicin (enterococci) Ampicillin + ceftriaxone (if aminoglycoside-resistant enterococci)	4 (gentamicin for first 2 wk)
Enterococci	Penicillin G + gentamicin OR Ampicillin + gentamicin (use if penicillin G is unavailable)	Vancomycin + gentamicin Ampicillin + ceftriaxone (if aminoglycoside-resistant enterococci)	4
Penicillin-susceptible <i>S. aureus</i>	Penicillin G	Oxacillin, nafcillin, cefazolin, or vancomycin (if β -lactam allergy)	
MSSA	Nafcillin or oxacillin $\pm$ gentamicin	Vancomycin or cefazolin	6 (gentamicin 3 mg/kg/day for 3–5 days)

Table 12. Antimicrobial Treatment of Endocarditis (*continued*)

Organism	Antimicrobial Therapy	Alternative Therapy	Duration (wk)
MSSA	Nafcillin or oxacillin ± gentamicin	Vancomycin or cefazolin	6 (gentamicin 3 mg/kg/day for 3–5 days)
MSSA in patient with prosthetic device or material	Nafcillin or oxacillin or cefazolin + rifampin + gentamicin		≥ 6 (gentamicin 3 mg/kg/day for 2 wk)
MRSA	Vancomycin	Daptomycin	4–6
MRSA in patient with prosthetic device or material	Vancomycin + rifampin + gentamicin		≥ 6 (gentamicin 3 mg/kg/day for 2 wk)
Vancomycin resistant <i>S. aureus</i>	Daptomycin		
HACEK organism	Ceftriaxone or ampicillin/sulbactam	Ampicillin + gentamicin	4
Gram-negative enteric bacilli	Ceftazidime, cefepime, or ceftriaxone + gentamicin (or alternative aminoglycoside based on susceptibility)	Piperacillin/tazobactam + gentamicin	≥ 6

MBC = minimum bactericidal concentration.

2. Patients with a β -lactam allergy
 - a. Streptococci: Vancomycin
 - b. Enterococci: Vancomycin plus gentamicin
 - c. Presence of prosthetic material: Vancomycin plus gentamicin
 - d. MSSA: Cefazolin with or without gentamicin (gentamicin for 3–5 days)

X. INTRA-ABDOMINAL INFECTIONS

A. Introduction

1. Uncomplicated: Involves inflammation of the gastrointestinal (GI) tract, but can progress to complicated infection
2. Complicated: Infection that extends beyond the GI tract and involves the peritoneum and is associated with abscess or peritonitis

B. Microbiology

1. Gram-negative Enterobacterales (*E. coli*, *Klebsiella*, *Proteus*, *Pseudomonas*)
2. Anaerobes (*Bacteroides*, *Clostridium*)
3. Gram-positive cocci (*Streptococcus*, *Enterococcus*)

C. Clinical Presentation

1. Acute onset of abdominal pain
2. Loss of appetite
3. Nausea and/or vomiting
4. Bloating
5. Abdominal rebound tenderness
6. Systemic symptoms (fever, tachycardia, tachypnea) may also be present.

D. Diagnosis

1. History and physical examination
2. CT scan is preferred imaging (especially for suspected acute appendicitis).
3. Ultrasonography
4. Intra-abdominal cultures (if drainage procedure performed)

E. Treatment

1. Fluid resuscitation should be initiated when the diagnosis of intra-abdominal infection is suspected and immediately if patients present with hypotension.
2. Treatment is based on origin and severity of infection.
 - a. Community-acquired infection
 - b. Health care–associated complicated infection
3. Empiric antimicrobial therapy should provide sufficient coverage against enteric gram-negative bacilli, anaerobes, and gram-positive streptococci.
 - a. Carbapenem (ertapenem, meropenem, imipenem/cilastatin)
 - b. β -Lactam/ β -lactamase inhibitor (piperacillin/tazobactam)
 - c. Third- or fourth-generation cephalosporin (ceftriaxone, ceftazidime, cefepime) plus metronidazole
 - d. Gentamicin or tobramycin plus metronidazole OR clindamycin with or without ampicillin
 - e. Ciprofloxacin plus metronidazole is an alternative to aminoglycoside-based regimens in patients with β -lactam allergies.
4. Empiric antifungal therapy is not routinely recommended unless *Candida* is grown from a culture.
 - a. Fluconazole is the agent of choice for *C. albicans*.
 - b. In neonates, empiric antifungal therapy with fluconazole is recommended if *Candida* is suspected.
 - c. Echinocandins (caspofungin, micafungin) are recommended in patients with fluconazole-resistant *Candida* spp. or in critically ill pediatric patients.
5. Oral step-down therapy
 - a. Second- or third-generation cephalosporin plus metronidazole
 - b. Amoxicillin/clavulanate
 - c. Fluoroquinolones (ciprofloxacin or levofloxacin) may be used for *Pseudomonas*, *Enterobacter*, *Citrobacter*, or *Serratia*.

XI. FUNGAL INFECTIONS

A. Introduction

1. Significant cause of morbidity and mortality in the United States
2. Increase in invasive fungal infections in children during the past few decades

B. Microbiology

1. *Candida* spp. – *C. albicans* and *C. parapsilosis* cause 80%–90% of neonatal candidiasis.
2. *Aspergillus* spp. – *A. fumigatus* is the most common species identified.

C. Risk Factors for Invasive Fungal Infection

1. Candidiasis
 - a. Immunosuppression
 - b. Prematurity/extremely low birth weight
 - c. Presence of indwelling catheters
 - d. Use of broad-spectrum antimicrobial agents
 - e. Parenteral nutrition

2. Aspergillosis
 - a. Hematologic malignancies
 - b. Stem cell and solid organ transplantation
 - c. Inherited immunodeficiencies
 - i. Chronic granulomatous disease
 - ii. Job syndrome
- D. Clinical Presentation
 1. Candidiasis – Fever
 2. Aspergillosis
 - a. Nonspecific: Fever
 - b. Pulmonary manifestation (cough, dyspnea, chest pain, hemoptysis)
 - c. Skin manifestation
- E. Diagnostic Evaluation
 1. Candidiasis
 - a. Blood culture: If positive in a neonate, perform lumbar puncture and dilated retinal examination.
 - b. Urine culture: If positive in a neonate, perform lumbar puncture and dilated retinal examination.
 - c. Peptide nucleic acid fluorescent in situ hybridization (PNA FISH)
 - d. Galactomannan test
 - e. β -D-glucan serum assay
 2. Aspergillosis
 - a. Blood culture
 - b. Galactomannan test
 - c. PCR tests
 - d. Chest radiograph
 - e. CT scan (to determine presence of halo sign or nodular lesion)
 - f. β -D glucan serum assay (in high risk patients)
 - g. Bronchoscopy only if invasive pulmonary aspergillosis is suspected
- F. Antifungal Prophylaxis in the Neonatal Intensive Care Unit
 1. Recommended in nurseries with a greater than 10% rate of invasive candidiasis
 2. Fluconazole, 3–6 mg/kg per dose orally or intravenously twice weekly for 6 weeks in neonates weighing less than 1000 g
- G. Treatment of Candidiasis
 1. Neonatal candidiasis
 - a. Antifungal therapy
 - i. Amphotericin B deoxycholate 1 mg/kg per dose intravenously once daily
 - ii. Fluconazole 25 mg/kg loading dose followed by 12 mg/kg once daily, if not on fluconazole prophylaxis
 - iii. Lipid formulation amphotericin B, 3–5 mg/kg per dose intravenously once daily (alternative, use with caution in UTIs, kidney infections, CNS infections, eye infections because of less-optimal penetration into these areas)
 - iv. In general, avoid echinocandins because of low concentrations in the CNS and urinary tract.
 - v. Flucytosine can be used for disseminated candidiasis with CNS or urinary tract involvement.
 - b. Central venous catheter removal
 - c. Treatment duration: 2 weeks after clearance of *Candida* from bloodstream and clinical signs of infection

2. Candidiasis in the pediatric patient
 - a. Echinocandin (moderately severe or severe illness)
 - i. Caspofungin 70 mg/m² per dose intravenously once daily on day 1, followed by 50 mg/m² per dose intravenously once daily
 - ii. Micafungin intravenously once daily (2–4 mg/kg/day, neonates 10–12 mg/kg/day)
 - iii. Anidulafungin intravenously once daily (infants, children, and adolescents: 3 mg/kg per dose intravenously once on day 1, followed by 1.5 mg/kg per dose intravenously once daily)
 - b. Fluconazole: Recommended for less severely ill patients or those with no recent azole exposure
 - c. Amphotericin B
 - i. Liposomal
 - ii. Lipid complex (ABLC)
 - iii. Conventional

H. Treatment of Invasive Aspergillosis

1. Voriconazole is first-line agent and superior to liposomal amphotericin B for response rate and survival
 - a. 9 mg/kg/dose intravenously every 12 hours for two doses, followed by 8 mg/kg/dose intravenously every 12 hours
 - i. Trough concentrations of more than 2 mcg/mL should be maintained.
 - ii. Children and adolescents weighing 50 kg or more should receive a loading dose of 6 mg/kg/dose intravenously every 12 hours for 2 doses, followed by 4 mg/kg/dose intravenously every 12 hours.
 - iii. Nonlinear kinetics are observed when transitioning from intravenous to oral. Formulations are not equivalent.
 - b. Adverse reactions: Visual disturbances, hepatotoxicity, rash, visual hallucinations
 - c. Monitoring: Liver function tests, ophthalmologic examinations, plasma concentrations
2. Itraconazole
 - a. Commonly used for management of aspergillosis in chronic granulomatous disease
 - b. 5 mg/kg per dose (maximum per dose 200 mg) orally twice daily
 - c. Erratic bioavailability: Solution is preferred, given its better bioavailability. Solution and capsules are not interchangeable. Measurement of plasma concentrations is recommended.
3. Posaconazole
4. Liposomal amphotericin B: 3–5 mg/kg intravenously once daily
5. Caspofungin
6. Micafungin
7. Isavuconazonium sulfate: Limited information in pediatric patients

XII. PARASITIC INFECTIONS

A. *Pediculus humanus capitis* (head louse)

1. Common infection in school-aged children 3–12 years of age; 6–12 million cases per year in the United States
2. Cause
 - a. Adult head louse
 - i. Female lives 3–4 weeks and can lay up to 10 eggs per day.
 - ii. Eggs attach to base of hair shaft until they hatch (8–12 days).
 - b. Spread from person-to-person by direct close contact
 - i. Head to head, sharing clothes or pillows
 - ii. Caregivers can become infected.

3. Diagnosis
 - a. Observation of live lice on the head and scalp; may need a lice or fine-tooth comb to detect
 - b. Empty egg casings (nits) are easily seen as white specks against darker hair.
 - c. All household members who come in close contact with the patient should be checked for the presence of lice and treated if lice is detected.
 4. Treatment
 - a. Nonprescription topical medications administered at diagnosis for one dose and may be repeated 7–10 days if needed
 - i. Permethrin 1%
 - (a) First-line treatment
 - (b) May be used in children older than 2 months
 - (c) Kills lice by causing nerve damage and paralysis through inhibition of sodium ion influx
 - ii. Pyrethrin: Opens sodium ion channels in neurons, which causes spasms and death of lice
 - b. Prescription topical medications
 - i. Benzyl alcohol 5%
 - (a) May be used in children 6 months and older
 - (b) Non-ovicidal, kills lice by asphyxiation
 - (c) Must be repeated in 7–10 days
 - ii. Ivermectin
 - (a) May be used in children 6 months and older
 - (b) Also available as an oral treatment
 - (c) Causes hyperpolarization of the nerve or muscle cells of lice by binding to chloride ion channels
 - iii. Malathion 0.5%
 - (a) May only be used in children older than 2 years
 - (b) Alternative to nonprescription products if resistance develops or treatment fails
 - (c) Cholinesterase inhibitor
 - iv. Spinosad 0.9%
 - (a) May only be used in children 6 months or older
 - (b) Non-ovicidal, kills lice by hyperexcitation and death by paralysis
 - v. Lindane is not recommended by the American Academy of Pediatrics for treatment of pediatric patients with lice.
 - (a) May cause systemic CNS toxicity and induce seizures
 - (b) Directly absorbed by parasites, resulting in nervous system stimulation, seizures, and death
- B. Scabies
1. Common infection worldwide and affects all ages, classes, races equally; 300 million cases worldwide
 2. Cause
 - a. Infestation of the human itch mite, *Sarcoptes scabiei* var. *hominis*, into the superficial layers of the skin
 - b. Spread from prolonged person-to-person contact or through outbreaks
 3. Clinical presentation
 - a. Intense pruritus that commonly worsens at night
 - b. Inflammatory pruritic papules or pustules on the skin that can appear as a faint zigzag pattern on the skin; commonly occurring on hands, wrists, feet, neck
 4. Diagnosis
 - a. Direct visualization of the mites or eggs in a skin scraping
 - b. Clinical signs and symptoms

5. Treatment
 - a. Prescription topical medications
 - i. Must be applied to the entire body and left on overnight, washed off after a minimum of 8 hours, and repeated in 1 week
 - ii. Permethrin 5% – First-line treatment for infants and children older than 2 months
 - iii. Topical sulfur 2%–10% ointment (for neonates)
 - iv. Spinosad 0.9% topical suspension (for patients 4 years and older)
 - b. Prescription oral medication: Ivermectin
 - i. Alternative to first-line topical agents
 - ii. 200 mcg/kg single dose for children weighing 15 kg or more
 - iii. Repeat in 10–14 days.
 - c. Environmental control – Wash bedding, towels, and clothing in hot water.

XIII. SEPSIS/SEPTIC SHOCK

- A. Guidelines for the Management of Severe Sepsis and Septic Shock
 1. New sepsis guidelines were released in 2020 for all patients older than 37 weeks' gestation at birth to 18 years of age with septic shock and other sepsis-associated organ dysfunction.
 2. Definitions
 - a. Septic shock is an infection leading to cardiovascular dysfunction (hypotension, need for vasoactive medications or impaired perfusion).
 - b. Sepsis-associated organ dysfunction is severe infection leading to cardiovascular and/or noncardiovascular organ dysfunction.
- B. Neonatal Sepsis
 1. Early-onset sepsis
 - a. Onset of symptoms within 72 hours of birth
 - b. Risk factors: Prematurity, very low birth weight (VLBW), prolonged rupture of the amniotic membranes, prolonged or traumatic labor, maternal chorioamnionitis, maternal UTI or group B *Streptococcus* colonization, meconium-stained amniotic fluid)
 - c. Incidence: 0.7–3.7 of 1000 live births (increased in VLBW infants: 8 of 1000 infants)
 - d. Common microorganisms: Group B *Streptococcus*, *L. monocytogenes*, *E. coli*, HSV
 2. Late-onset sepsis
 - a. Onset of symptoms after the first 3 days of life
 - b. Risk factors: Presence of umbilical or other central venous catheters, presence of endotracheal tubes
 - c. Incidence: 0.5–1.8 of 1000 live births (higher incidence of meningitis)
 - d. Common microorganisms: Coagulase-negative *Staphylococcus*, *S. aureus*, *Enterococcus*, *Klebsiella* spp., *P. aeruginosa*, *Enterobacter* spp., *Candida* spp.
 3. Clinical presentation
 - a. Apnea
 - b. Heart rate instability (bradycardia or tachycardia may occur)
 - c. Respiratory distress or cyanosis
 - d. Temperature instability (hypothermia or hyperthermia may occur)
 - e. Feeding intolerance or abdominal distention
 - f. Bloody stools
 - g. Lethargy
 - h. Bulging fontanelle
 - i. Seizure
 - j. Hypotension

4. Diagnostic evaluation
 - a. Complete blood cell count (CBC)
 - i. Platelet count less than 100,000/mm³
 - ii. WBC less than 5 or greater than 12×10^3 cells/mm³
 - b. Immature/total neutrophil ratio (greater than 0.2 suggestive of infection)
 - c. CRP (greater than 1 mg/dL suggestive of infection)
 - d. Blood cultures
5. Empiric treatment (Table 13)
 - a. Early onset: Ampicillin plus gentamicin
 - i. Treatment duration is 48 hours for patients presenting in the first month of life with signs and symptoms of infection with negative blood and CSF cultures.
 - ii. Treatment can be extended to 7 days for “clinical sepsis.” Patients with signs and symptoms of sepsis with negative culture results (especially if antibiotics given before blood/CSF cultures obtained)
 - b. Late onset: Vancomycin plus gentamicin

Table 13. Recommended Pathogen-Directed Treatment of Neonatal Sepsis

Microorganism	Treatment	Suggested Therapy Duration
<i>Listeria</i>	Ampicillin + gentamicin	21 days
GBS	Ampicillin + gentamicin	10 days
<i>E. coli</i>	Gentamicin	10 days
<i>Enterococcus</i>	Ampicillin + gentamicin	10 days
HSV	Acyclovir	14–21 days
<i>Pseudomonas</i>	Cefepime, ceftazidime, meropenem, piperacillin/tazobactam + tobramycin	10 days
Coagulase-negative <i>Staphylococcus</i>	Vancomycin (oxacillin resistant) OR nafcillin or oxacillin (oxacillin sensitive)	14 days
MSSA	Nafcillin or oxacillin	14 days
<i>Candida</i>	Amphotericin B	21 days (can switch to azole if sensitive)

HSV = herpes simplex virus.

- C. Pediatric Sepsis (see PICU chapter)
 1. Introduction: Spectrum of disorders that result from infection
 2. Clinical presentation
 - a. SIRS (systemic inflammatory response syndrome)
 - b. Hyperthermia or hypothermia
 - c. Tachypnea
 - d. Tachycardia
 3. Microorganisms: Bacteria, viruses, fungi, parasites

Bacteria:

 - a. *S. pneumoniae*
 - b. *S. aureus*
 - c. *E. coli*
 - d. *N. meningitidis*

4. Diagnosis
 - a. CBC
 - b. Blood, urine, CSF culture
 - c. Coagulation measurements (prothrombin time [PT], partial thromboplastin time [PTT], international normalized ratio [INR])
 - d. BMP (basic metabolic panel)
 - e. Electrolytes
 - f. Inflammatory markers (CRP, ESR, procalcitonin)
 - g. Chest radiograph
5. Treatment definitions
 - a. Empiric: Initial antimicrobial therapy for suspected infection in the absence of a definitive pathogen
 - b. Broad-spectrum: Antimicrobial regimen with activity against multiple pathogens
 - i. According to local, regional, or national pathogen epidemiology and patient risk factors
 - ii. Community-acquired sepsis: Third-generation cephalosporin may be used (e.g., ceftriaxone) with or without vancomycin if suspected MRSA or ceftriaxone-resistant pneumococci
 - iii. Immunocompromised patients: Antipseudomonal third-generation cephalosporin, ceftazidime, meropenem, imipenem/cilastatin, or piperacillin/tazobactam
 - iv. Intra-abdominal source of infection: Expand empiric coverage to include coverage against anaerobic bacteria.
 - c. Targeted/definitive: Antimicrobial regimen targeted to specific pathogen(s) after microbiological identification
 - i. Single or multiple agents can be used.
 - ii. Narrow spectrum of activity from empiric regimen
6. Synergistic antimicrobial regimens (double coverage): Not routinely recommended in the newest guidelines except for in certain clinical situations
 - a. Confirmed or suspected group B *Streptococcus*
 - b. Device-associated infection
 - c. Carbapenem-resistant Enterobacteriaceae infection
7. De-escalation of antimicrobial therapy
 - a. Daily assessment
 - b. Recommend de-escalation depending on clinical improvement and/or resolution of infection.
8. Duration: Guided by site of infection, clinical response, microbial etiology, and source control

XIV. TUBERCULOSIS

- A. Introduction and Epidemiology – Incidence in the United States is decreasing overall but still results in 2 million deaths per year worldwide.
 1. Children younger than 14 years have the lowest incidence in the United States.
 2. In the United States, more than half of cases occur in foreign-born individuals.
- B. Etiology
 1. Infection caused by *Mycobacterium tuberculosis* – Acid-fast bacilli
 2. Spread through aerosolized droplets from an infected person
- C. Clinical Presentation
 1. Signs and symptoms: Weight loss, fatigue, productive cough, fever, night sweats, hemoptysis
 2. Elevated WBC with a lymphocyte predominance

D. Diagnosis

1. PPD (tuberculin skin test)
 - a. Intradermal test
 - b. Positive if area of induration around injection site after 48–72 hours is 5 mm or greater
2. Radiographic findings: Cavitory upper lobe lesion on chest radiograph
3. Acid-fast bacilli sputum culture – Collect sputum daily in the morning for 3 consecutive days.
4. Interferon-gamma release assay in children 5 years and older with suspected latent TB

E. Latent TB vs. Active TB Disease

1. Latent TB
 - a. Patients have presence of bacteria in their body, but they are not infectious or contagious because the bacteria are not active.
 - b. Positive PPD
 - c. Negative chest radiograph and sputum cultures
 - d. Asymptomatic
 - e. Can progress to TB disease if bacteria become active
2. Active TB disease
 - a. Presence of active TB bacteria
 - b. Patients can spread the disease to other individuals; however, infants and younger children with primary TB disease are rarely contagious. Lack of contagious forms of disease because of recent acquisition of the organism in younger children
 - c. Positive PPD
 - d. Abnormal chest radiograph and sputum cultures may be positive.
 - e. Presence of signs and symptoms

F. Treatment

1. Latent TB infection
 - a. Once-weekly isoniazid plus rifapentine for 3 months (for patients greater than 2 years old)
 - b. Daily rifampin for 4 months (any age)
 - c. Daily isoniazid plus rifampin for 3 months (any age)
 - d. Alternative: Daily isoniazid for 6 or 9 months (any age)
2. Active TB disease
 - a. Intensive phase with a four-drug combination: Rifampin plus isoniazid plus pyrazinamide plus ethambutol for 2 months
 - b. Continuation phase with a two-drug regimen: Isoniazid plus rifampin for 4–7 months
3. DOT (direct observation therapy) is recommended for all children and adolescents with TB disease and latent TB infection.
4. Routine hepatic monitoring is required for all agents.
5. Medications
 - a. Isoniazid
 - i. Early bactericidal activity
 - ii. Main adverse effects are liver abnormalities and peripheral neuropathy.
 - iii. Recommend treatment with vitamin B₆ (pyridoxine) 25–50 mg/day to help prevent neuropathy.
 - b. Rifampin
 - i. Should not be used as monotherapy for treatment of active TB because resistance develops rapidly
 - ii. Counsel on adverse effect of orange discoloration of bodily fluids and sensitivity to sun.
 - iii. Rifabutin and rifapentine are newer rifamycins that may be used in patients unable to tolerate rifampin.

- c. Pyrazinamide
 - i. Bacteriostatic
 - ii. Only used in combination therapy for treatment
 - iii. Most common adverse effect is joint pain.
 - iv. No longer recommended for latent TB disease due to risk of hepatotoxicity
- d. Ethambutol
 - i. Bacteriostatic
 - ii. Used to prevent the emergence of rifampin resistance
 - iii. Main adverse effect is retrobulbar neuritis that leads to decreased visual activity.
- e. Second-line agents
 - i. Cycloserine
 - ii. Ethionamide
 - iii. Levofloxacin or moxifloxacin
 - iv. Streptomycin
 - v. Amikacin/kanamycin
 - vi. Capreomycin
 - vii. Bedaquiline
6. Drug-resistant TB
 - a. Suspect if sputum is AFB (acid-fast bacillus) positive after 1–2 months of therapy or positive cultures after 2–4 months of therapy
 - b. Multidrug-resistant
 - i. Resistant to at least isoniazid and rifampin
 - ii. Treatment regimen will include 4–5 agents and should be individually tailored.
 - c. Extensively drug-resistant
 - i. Resistant to isoniazid and rifampin plus resistant to any fluoroquinolone and at least one of the three second-line agents (amikacin, kanamycin, or capreomycin)
 - ii. Treatment regimen will include five medications for treatment and individually tailored based on drug susceptibility testing.

XV. SEXUALLY TRANSMITTED DISEASES

- A. Introduction – Disease acquired or transmitted through sexual activity. Prevention counseling recommended for all sexually active adolescents and adults at risk of sexually transmitted diseases (STDs)
- B. Preventive Strategies
 1. Abstinence is the most reliable way to avoid STDs
 2. Preexposure vaccinations help prevent transmission of human papillomavirus (HPV), hepatitis A virus, and hepatitis B virus
 3. Condoms
- C. Recommended Screening of Special Populations
 1. Pregnant women
 2. Adolescents
- D. Genital HSV Infection
 1. Chronic, lifelong viral infection caused by either HSV-1 or HSV-2 (most sexually transmitted cases)
 2. Affects about 50 million people in the United States

3. Diagnosis
 - a. Clinical presentation of painful vesicular lesions
 - b. Cell culture and HSV PCR assay
 4. Treatment
 - a. Acyclovir 400 mg orally three times daily or 200 mg orally five times daily for 7–10 days
 - b. Fanciclovir 250 mg orally three times daily for 7–10 days
 - c. Valacyclovir 1000 mg orally twice daily for 7–10 days
 5. Suppressive antiviral therapy is recommended (with one of the agents above) to prevent recurrence.
 6. Neonatal herpes
 - a. Treat with intravenous acyclovir 20 mg/kg/dose every 8 hours for 14 days if limited to skin and mucous membranes or 21 days if disseminated or involving CNS
 - b. For more information, see the chapter titled “Neonatology.”
- E. Chlamydia
1. Caused by *Chlamydia trachomatis*
 2. Annual screening of all sexually active women 25 years and younger is recommended.
 3. Clinical presentation: Inguinal unilateral lymphadenopathy (if presence of lymphogranuloma venereum), cervicitis, urethritis
 4. Treatment
 - a. Treatment for both gonorrhea and chlamydia is recommended unless one can specifically be ruled out.
 - b. Children weighing less than 45 kg: Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided four times daily for 14 days
 - c. Children and adolescents 8 years and older: Preferred: Doxycycline 100 mg orally twice daily for 7 days. Alternative: Azithromycin 1000 mg orally once
 5. Chlamydial infections in infants
 - a. Most common clinical presentation is conjunctivitis (ophthalmia neonatorum).
 - b. Atypical pneumonia can occur in infants 1–3 months of age.
 - c. Treatment
 - i. Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided four times daily for 14 days
 - ii. Azithromycin 20 mg/kg/day orally once daily for 3 days
- F. Syphilis
1. Systemic disease caused by *Treponema pallidum*
 2. Clinical presentation
 - a. Primary infection: Chancre
 - b. Secondary infection: Rash, mucocutaneous lesions, lymphadenopathy
 - c. Neurologic infection: Meningitis, altered mental status
 - d. Tertiary infection: Cardiac lesions
 3. Latent syphilis – No clinical manifestations with positive serology
 4. Diagnosis
 - a. PCR testing (RPR [rapid plasma reagin])
 - b. Infants older than 1 month should have a lumbar puncture to rule out neurosyphilis.
 5. Treatment
 - a. Benzathine penicillin G 50,000 units/kg intramuscularly (maximum 2.4 million units) as a single dose
 - b. For more information, see the Neonatology chapter.

6. Congenital syphilis – refer to the Neonatology section
 - a. Treatment during first month of life: Penicillin G 50,000 units/kg per dose intravenously every 12 hours for the first week of life, then every 8 hours thereafter for 10 days
 - b. Treatment in older infants and children: Penicillin G 200,000–300,000 units/kg/day intravenously divided every 4–6 hours for 10 days
 - c. Patients with penicillin allergy should undergo antibiotic desensitization.
 - d. For more information, see the Neonatology chapter.
- G. Gonococcal Infections
1. Second most common bacterial STD, with 700,000 new cases every year in the United States
 2. Caused by *N. gonorrhoeae*
 3. Most common clinical presentation in infants is conjunctivitis (ophthalmia neonatorum).
 - a. Treatment for both gonorrhea and chlamydia is recommended unless one can specifically be ruled out.
 - b. Infants with ophthalmia neonatorum or as prophylaxis in infants born to mothers with untreated infection
 - i. Ceftriaxone 25–50 mg/kg per dose intravenously or intramuscularly × 1 dose (maximum dose 250 mg)
 - c. Infants with disseminated gonococcal infection or scalp abscess
 - i. Ceftriaxone 50 mg/kg per dose intravenously once daily for 7 days (10–14 days if meningitis)
 - d. Children weighing 45 kg or less
 - i. Ceftriaxone 25–50 mg/kg/dose intramuscularly or intravenously once (maximum dose 250 mg)
 - ii. Bacteremia or arthritis: Ceftriaxone 50 mg/kg/dose intramuscularly or intravenously once daily for 7 days (maximum dose 2000 mg)
 - e. Children weighing more than 45 kg
 - i. Ceftriaxone 500 mg intramuscularly once; 1000 mg is recommended for patients 150 kg or more
 - ii. Gentamicin and cefixime may be used as alternative in uncomplicated infections if ceftriaxone is unavailable
 - iii. Bacteremia or arthritis: Ceftriaxone 50 mg/kg/dose intramuscularly or intravenously once daily for 7 days (maximum dose 1000 mg)
- H. Pelvic Inflammatory Disease
1. Inflammation of the upper female genital tract
 2. Usually caused by *N. gonorrhoeae* or *C. trachomatis*
 3. Clinical presentation: If pelvic or lower back pain with no other cause of illness and if presence of cervical motion tenderness or uterine or adnexal tenderness
 4. Treatment
 - a. Inpatient treatment
 - i. Cefoxitin 2000 mg intravenously every 6 hours plus doxycycline 100 mg orally or intravenously every 12 hours
 - ii. Discontinue parenteral treatment 24 hours after clinical improvement, and continue doxycycline orally for 14 days.
 - iii. Alternative: Clindamycin 900 mg intravenously every 8 hours plus gentamicin 3–5 mg/kg/day
 - b. Outpatient treatment
 - i. Ceftriaxone (500 mg if <150 kg or 1000 mg if ≥150 kg) intramuscularly once plus doxycycline 100 mg orally twice daily for 14 days plus or minus metronidazole 500 mg orally twice daily for 14 days
 - ii. The use of fluoroquinolones should not be recommended because of the emergence of quinolone-resistant strains of *N. gonorrhoeae*.

XVI. SURGICAL PROPHYLAXIS

A. Introduction

1. Pediatric-specific guidelines do not exist; recommendations are based on expert opinion.
2. Preoperative dosing should occur within 60 minutes before the incision.
3. Additional intraoperative doses are needed, depending on the length of the procedure and the half-life of the antibiotic used.
4. Postoperative prophylaxis is not routinely recommended. Continue for a maximum of 24 hours post-procedure if used.

B. Classification of Surgical Procedures

1. Clean: Elective with no break in technique and no entry in the respiratory, GI, or genitourinary tracts or in the oropharyngeal cavity
2. Clean contaminated: Entry in the respiratory, GI, genitourinary, or biliary tracts or oropharyngeal cavity without unusual contamination. Clean procedures with a minimal break in technique
3. Contaminated: Fresh traumatic wounds, gross spillage from the GI tract, major break in technique, or incisions encountering acute, nonpurulent inflammation
4. Dirty: Procedures involving previous traumatic wounds, perforated viscera, or clinically evident infection

C. Agents Used for Specific Surgical Procedures (Table 14 and Table 15)

Table 14. Surgical Antimicrobial Prophylaxis

Type of Procedure	First-line Antimicrobial	Alternative Antimicrobials for β -Lactam Allergy
Cardiac	Cefazolin, cefuroxime	Clindamycin, vancomycin
Video-assisted thoracoscopic surgery	Cefazolin, ampicillin/sulbactam	Clindamycin, vancomycin
Gastroduodenal	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam
Biliary tract, open procedure	Cefazolin, cefoxitin, ceftriaxone, ampicillin/sulbactam	Clindamycin or vancomycin + aminoglycoside or aztreonam
Appendectomy for uncomplicated appendicitis	Cefoxitin, cefazolin + metronidazole	Clindamycin + aminoglycoside or aztreonam OR metronidazole + aminoglycoside
Non-obstructed small intestine	Cefazolin	Clindamycin + aminoglycoside or aztreonam
Obstructed small intestine	Cefoxitin, cefazolin + metronidazole	Metronidazole + aminoglycoside
CSF shunt surgery or implantation of intrathecal pumps	Cefazolin	Clindamycin, vancomycin
Ophthalmic	Topical neomycin-polymyxin B-gramicidin or moxifloxacin	
Spinal surgery (with or without instrumentation)	Cefazolin	Clindamycin, vancomycin

Table 14. Surgical Antimicrobial Prophylaxis (*continued*)

Type of Procedure	First-line Antimicrobial	Alternative Antimicrobials for β -Lactam Allergy
Implantation of internal fixation devices	Cefazolin	Clindamycin, vancomycin
Urologic	Cefazolin	Clindamycin, vancomycin
Vascular	Cefazolin	Clindamycin, vancomycin
Heart, lung, or heart-lung transplantation	Cefazolin	Clindamycin, vancomycin
Liver transplantation	Piperacillin/tazobactam	Clindamycin or vancomycin + aminoglycoside or aztreonam
Plastic surgery	Cefazolin	Clindamycin or vancomycin + aminoglycoside or aztreonam

Table 15. Recommended Dosing for Agents Used for Surgical Prophylaxis^a

Antimicrobial	Dose	Re-dosing Interval from Time of Initial Preoperative Dose
Ampicillin/sulbactam	50 mg/kg of ampicillin component	2
Ampicillin	50 mg/kg	2
Aztreonam	30 mg/kg	4
Cefazolin	30 mg/kg	4
Cefuroxime	50 mg/kg	4
Ceftriaxone	50 mg/kg	N/A
Clindamycin	10 mg/kg	6
Gentamicin	2.5 mg/kg	N/A
Metronidazole	15 mg/kg (7.5 mg/kg in neonates weighing < 1200 g)	N/A
Piperacillin/tazobactam	Infants 2–9 mo: 80 mg/kg of piperacillin component Children > 9 mo: 100 mg/kg of piperacillin component	2
Vancomycin	15 mg/kg	N/A

^aMax dosing should not exceed adult dosing.

N/A = not applicable.

Patient Case

Questions 10 and 11 pertain to the following case.

G.T. is a 5-year-old boy (weight 21.6 kg) with a medical history significant for hypoplastic left heart syndrome and recurrent otitis media. He presents after two surgical procedures to correct the congenital heart defect and is admitted today for his third procedure (Fontan). His medications are as follows: furosemide 10 mg orally twice daily and chlorothiazide 25 mg orally twice daily. He is allergic to amoxicillin (urticaria).

10. Which surgical prophylactic strategy is most appropriate for G.T. before his surgery?
 - A. Administer cefazolin 650 mg intravenously within 60 minutes of first incision.
 - B. Administer cefoxitin 650 mg intravenously within 60 minutes of first incision.
 - C. Administer clindamycin 220 mg intravenously within 120 minutes of first incision.
 - D. Administer vancomycin 320 mg intravenously within 120 minutes of first incision.
11. During the Fontan procedure, G.T. had difficulty being transitioned off cardiopulmonary bypass. Therefore, the surgery took 4 hours rather than 3 hours. Which best describes when the antibiotic should be re-dosed intraoperatively in this patient?
 - A. Does not need to be re-dosed.
 - B. 2 hours after initial preoperative dose.
 - C. 4 hours after initial preoperative dose.
 - D. 6 hours after initial preoperative dose.

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ANSWERS AND EXPLANATIONS FOR PATIENT CASES

1. Answer: B

Because viruses cause 40%–75% of AOM cases, the clinical practice guidelines for AOM diagnosis and management recommend observation and pain management for certain individuals (patients with mild symptoms and if mild symptoms and unilateral and 6–23 months of age). This patient is 3 years old and has mild ear pain and a low-grade fever. Therefore, observation and pain management are appropriate (Answer B is correct). If antibiotic therapy were used, cefdinir would be an appropriate choice because of the patient's history of allergy to amoxicillin. However, this patient should only be observed and not treated (Answer A is incorrect). Azithromycin is no longer recommended in the latest guidelines (Answer C is incorrect). Ceftriaxone intramuscular therapy is an alternative treatment option for patients who do not respond to first-line antibiotic therapy after 48–72 hours. Therefore, this patient is not a candidate for ceftriaxone (Answer D is incorrect).

2. Answer: C

Vancomycin would be the first-line agent for this patient whose outpatient therapy had failed and whose culture is growing MRSA (Answer C is correct). Clindamycin is not appropriate because the sensitivities show a positive D-test, which could result in inducible bacterial resistance and possibly treatment failure (Answer B is incorrect). Cefazolin is the agent of choice for empiric therapy when there is low suspicion of MRSA and for treatment of confirmed MSSA (Answer A is incorrect). Linezolid is an alternative to vancomycin for MRSA. However, it would be less cost-effective than vancomycin (Answer D is incorrect).

3. Answer: D

Sulfamethoxazole/trimethoprim is the best oral treatment option for this patient because the organism is sensitive to this agent, the agent can safely be used for patients of this age, and the agent is cost-effective (Answer D is correct). Clindamycin cannot be used because the D-test was positive (Answer A is incorrect). Doxycycline could be a treatment option for an older pediatric patient (older than 8 years); however, this patient is only 16 months old, and doxycycline is not indicated in this age group (Answer B is incorrect). Linezolid could be a treatment option for MRSA and

other multidrug-resistant gram-positive organisms. However, it is costly and therefore not the first choice if other alternatives are available (Answer C is incorrect).

4. Answer: C

The most common microorganisms for osteomyelitis in this age group are *S. aureus* and *S. pyogenes*. A penicillinase-resistant penicillin or first-generation cephalosporin is the first-line treatment option if the risk of MRSA is low. Cefazolin is the best option for this patient because he has no significant medical history or risk factors for MRSA (Answer C is correct). Ceftriaxone is not a first-line monotherapy agent unless *Salmonella* osteomyelitis (presence of sickle cell disease) or infectious arthritis caused by *N. gonorrhoeae* is suspected (Answer A is incorrect). Ceftriaxone can be used in combination with clindamycin when *K. kingae* is suspected (usually in younger children with concomitant respiratory tract infection symptoms). Ciprofloxacin is an alternative agent for patients with a penicillin allergy and a suspected *Salmonella* infection (Answer B is incorrect). Clindamycin is indicated empirically if the patient has an allergy to penicillin or if there is a high suspicion of a resistant gram-positive organism or a positive patient or family history of MRSA (Answer D is incorrect).

5. Answer: B

The length of therapy for osteomyelitis caused by MSSA should be 4–6 weeks and can be completed with a combination of intravenous and oral therapy in patients without a complicated course or resistant organism (Answer A is incorrect). First-line treatment of MSSA osteomyelitis would be an oral penicillinase-resistant penicillin (dicloxacillin) or a first-generation cephalosporin (cephalexin) (Answer B is correct). Ciprofloxacin can be used to continue treatment of *Salmonella* osteomyelitis (Answer C is incorrect). Linezolid should be reserved for the treatment of osteomyelitis caused by resistant gram-positive organisms (Answer D is incorrect).

6. Answer: B

Empiric therapy for bacterial meningitis in this age group includes vancomycin and a third-generation cephalosporin. Definitive therapy should be guided

by the presence of specific microorganisms. Because this patient has *N. meningitidis*, it is appropriate to discontinue vancomycin and continue ceftriaxone (Answer B is correct). Vancomycin should only be continued for definitive treatment of a resistant gram-positive organism (Answer A is incorrect). Rifampin can be used in combination with ceftriaxone and vancomycin for the treatment of *S. pneumoniae* meningitis when the ceftriaxone MIC is intermediate (Answer C is incorrect). Penicillin is first line for the treatment of proven *S. pneumoniae* with a penicillin MIC less than 0.06 mcg/mL and is usually not used in combination with rifampin (Answer D is incorrect).

7. Answer: D

Chemoprophylaxis is recommended for individuals in close contact with patients who have *N. meningitidis* meningitis (Answer B is incorrect). Appropriate agents are rifampin, ciprofloxacin, or ceftriaxone (Answer D is correct). Although ceftriaxone can be used for chemoprophylaxis, only a single dose is recommended for 1 day, not 7 days (Answer A is incorrect). Answer C is incorrect; although the quadrivalent meningococcal conjugate vaccine intramuscularly $\times$ 1 dose is recommended in the routine CDC immunization schedule, given this patient's age, it would not be appropriate for chemoprophylaxis.

8. Answer: C

This patient can receive oral antimicrobial therapy as an outpatient. First-line empiric therapy for a presumed UTI includes sulfamethoxazole/trimethoprim, amoxicillin/clavulanate, or a cephalosporin. The agent of choice should be based on local susceptibility patterns to these agents (Answer C is correct). Nitrofurantoin should not be used for empiric treatment of a UTI in a febrile child younger than 2 years because it does not maintain therapeutic serum concentrations in the blood. (Answer B is incorrect). Ciprofloxacin is reserved for oral treatment of complicated UTIs secondary to *P. aeruginosa* (Answer A is incorrect). Amoxicillin/clavulanate is preferred to amoxicillin because of the potential for β -lactamase-producing gram-negative organisms. In addition, the high dose listed (80 mg/kg/day) is not required for treating a UTI (Answer D is incorrect).

9. Answer: B

Ceftriaxone (or another third-generation cephalosporin) is considered first-line therapy for the management of pyelonephritis. It also has the advantage of being given once daily (Answer B is correct). Aminoglycosides are also recommended, but not in combination with ampicillin (Answer C is incorrect). Ciprofloxacin and piperacillin/tazobactam should be reserved for resistant organisms (Answers A and D are incorrect).

10. Answer: D

Cefazolin is the first-line agent recommended before cardiac surgical procedures. However, this patient has an allergic reaction to amoxicillin (urticaria). Cephalosporins (cefazolin and cefoxitin) should not be used in patients with type I, immunoglobulin (Ig) E-mediated allergic reactions to penicillin (Answer A is incorrect). In addition, cefoxitin is not recommended before a cardiac procedure (Answer B is incorrect). Alternative agents recommended for patients with a β -lactam allergy include clindamycin and vancomycin. Vancomycin is the correct choice for this patient because it should be administered 120 minutes before incision given its prolonged infusion time (Answer D is correct). Clindamycin can be given within 60 minutes (Answer C is incorrect).

11. Answer: A

Because of its long elimination half-life, vancomycin need not be re-dosed during surgical procedures that take longer than expected (Answer A is correct). Cefazolin would need to be re-dosed 4 hours after the initial preoperative dose (Answer C is incorrect). Like vancomycin, clindamycin would not need to be re-dosed if the surgery took 4 hours because it is not recommended to re-dose until 6 hours after the original dose (Answer D is incorrect). There is no recommendation to re-dose antibiotics within 2 hours (Answer B is incorrect).

ANSWERS AND EXPLANATIONS FOR SELF-ASSESSMENT QUESTIONS

1. Answer: B

Antibiotic therapy is appropriate for this patient because he is younger than 24 months and has bilateral signs and symptoms. Therefore, observation should not be considered (Answer D is incorrect). First-line therapy for a first-time AOM infection is high-dose amoxicillin (80–90 mg/kg/day divided twice daily) (Answer B is correct). Adding clavulanate to amoxicillin is an alternative treatment option if patients do not respond to initial therapy or if symptoms are more severe. Adding clavulanate increases the risk of diarrhea (Answer A is incorrect). Ceftriaxone is an alternative for patients with a β -lactam allergy or if a patient does not respond to first-line antibiotic treatment within 48–72 hours. However, the dose is 50 mg/kg/dose, not 75 mg/kg/dose as listed (Answer C is incorrect).

2. Answer: B

A penicillinase-penicillin such as nafcillin should be considered first line in patients with cellulitis because the most common organism is *S. aureus* (Answer B is correct). Depending on the geographic incidence of MRSA, empiric therapy should consist of clindamycin or possibly vancomycin. Doxycycline can be considered an option for this patient for the definitive treatment of a cellulitis caused by MRSA once sensitivities are known, but it should not be used empirically (Answer A is incorrect). Meropenem or ampicillin/sulbactam are considered broad-spectrum antibiotics and would be used if anaerobic bacteria were suspected (Answers C and D are incorrect).

3. Answer: D

The only recommended agent for the treatment of influenza in this 2-year-old patient is oseltamivir (Answer D is correct). Zanamivir is indicated for patients 7 years and older (Answer A is incorrect). Ribavirin is not indicated for the treatment of influenza A, but it has been used in the treatment of RSV (Answer C is incorrect). Amantadine and rimantadine are FDA label approved for a 2-year-old for the treatment and prophylaxis of influenza A. However, the CDC does not currently recommend these agents because of the increased resistance that occurs with them (Answer B is incorrect).

4. Answer: C

For the treatment of bacterial meningitis caused by *S. pneumoniae* that is non-susceptible to penicillin but sensitive to a third generation cephalosporin, the guidelines recommend monotherapy with a third-generation cephalosporin or ceftriaxone (answer C is correct). Rifampin is indicated for cephalosporin-intermediate or resistant strains in combination with vancomycin and a third generation cephalosporin which this patient does not have (answer D is incorrect). If rifampin is added, ceftriaxone should be continued (answer B is incorrect). It is not appropriate to continue vancomycin and ceftriaxone unless the strain is highly resistant (MIC greater than or equal to 2 mcg/mL) to penicillin (Answer A is incorrect).

5. Answer: B

Geographic resistance patterns are important to consider when selecting empiric treatment of possible osteomyelitis. First-line agents in a geographic area with a high MRSA resistance rate include clindamycin and vancomycin. Vancomycin is not necessary in this patient because the local clindamycin resistance is less than 10% (Answer C is incorrect). Therefore, clindamycin should be the empiric agent of choice. Ceftriaxone is appropriate to add for this patient because of the suspicion of *K. kingae* (given the presence of upper respiratory symptoms). Clindamycin does not provide coverage against that organism (Answer B is correct). Cefazolin would be an appropriate first-line empiric agent if the local MRSA resistance pattern were less than 10%, but it is not recommended to be combined with clindamycin (Answer A is incorrect). Cefazolin may be added to vancomycin for empiric treatment of possible *S. aureus* bacteremia; however, this combination does not provide coverage against *K. kingae* (Answer D is incorrect).

6. Answer: C

Necrotizing fasciitis caused by *S. pyogenes* should be treated with a combination of penicillin G and clindamycin. Combination therapy with clindamycin is recommended because it can neutralize the exotoxin produced by streptococcal species and decrease cytokine production (Answer C is correct). Vancomycin can be considered an alternative in a patient with a β -lactam allergy (Answer A is incorrect). Penicillin monotherapy would provide inadequate coverage against any possible toxin production (Answer B is incorrect). Clindamycin

monotherapy would provide inadequate coverage against potential GAS-resistant strains (Answer D is incorrect).

7. Answer: C

The patient presents with laryngotracheitis, or croup. First-line treatment is a combination of nonpharmacologic management (humidified O₂) and a combination of two pharmacologic agents to decrease the airway edema (Answer D is incorrect). Racemic epinephrine has direct α -agonist activity and causes local vasoconstriction. Dexamethasone acts as a potent anti-inflammatory agent that reduces tissue edema (Answer C is correct). Dexamethasone has been shown superior to nebulized budesonide and has a faster onset of action and longer duration of action (Answer A is incorrect). There is no benefit to the combination of dexamethasone and nebulized budesonide for the treatment of croup (Answer B is incorrect).

8. Answer: A

Renal bladder ultrasonography is indicated in febrile infants with UTIs to detect the presence of any anatomic abnormalities that require additional evaluation and can show whether there is renal parenchymal involvement for this patient with suspected pyelonephritis (Answer A is correct). Vesicoureteral voiding cystography is no longer recommended in the UTI guidelines after the first febrile UTI unless ultrasonography reveals hydronephrosis (Answer B is incorrect). In addition, antimicrobial prophylaxis is no longer indicated after the first febrile UTI in infants; however, antimicrobial prophylaxis may be considered if the UTI recurs (Answer C is incorrect). A urine culture should be obtained if this patient did not have one on initial presentation. However, although suprapubic aspiration provides the highest sensitivity for the presence of bacteria, it is not practical. Instead, a urine culture can routinely be obtained by a catheter (Answer D is incorrect).

9. Answer: B

Empiric management of a patient with possible *S. aureus* endocarditis is a penicillinase-resistant penicillin with or without gentamicin for synergy. Vancomycin is an alternative for a patient with prosthetic material and if there is high suspicion of MRSA. The patient's medical history and the presence of the Broviac catheter place him at higher risk of MRSA (Answer B is correct). Penicillin G with or without gentamicin is appropriate for the treatment of streptococcal species (Answer A is incorrect). Ampicillin and ceftriaxone in combination

with gentamicin are used in the management of endocarditis caused by the HACEK organisms (Answers C and D are incorrect).

10. Answer: C

The best management of a central venous catheter infection caused by coagulase-negative *S. aureus* is vancomycin in combination with an antibiotic lock for 10–14 days if the infection is uncomplicated for short- or long-term catheter types OR if the catheter is needed long term and the infection is uncomplicated (Answer C is correct). An alternative regimen would be removal of the catheter and systemic antibiotics for 5–7 days if the catheter were only needed short term. Because of the patient's complicated history and the need for the continuation of the catheter for parenteral nutrition, it is not recommended to remove the catheter at this time (Answer D is incorrect). Vancomycin with or without rifampin for 5–7 days can be considered if the catheter is only needed short term and is to be removed (Answers A and B are incorrect).

11. Answer: B

Management of active TB disease is a four-drug combination for 2 months with rifampin, pyrazinamide, isoniazid, and ethambutol (Answer B is correct). A two-drug regimen (isoniazid and rifampin) can be considered for latent TB; however, this patient has active signs and symptoms (Answer A is incorrect). Rifampin plus pyrazinamide was previously an alternative two-drug combination for latent TB, but is no longer recommended (Answer C is incorrect). There is no role for clarithromycin in the management of TB; however, it does have coverage against atypical mycobacteria (Answer D is incorrect).

12. Answer: D

This patient has a possible intra-abdominal infection. The first-line empiric regimen should provide coverage against gram-positive streptococci, enteric gram-negative bacilli, and anaerobes. The combination of cefazolin and metronidazole does not provide adequate gram-negative coverage (Answer A is incorrect). Ampicillin plus gentamicin does not provide adequate anaerobic coverage (Answer B is incorrect). Ceftriaxone plus tobramycin does not provide adequate anaerobic coverage (Answer C is incorrect). Clindamycin plus gentamicin provides coverage for streptococci and anaerobes (clindamycin) and enteric gram-negative organisms (gentamicin) (Answer D is correct).

HEMATOLOGY AND ONCOLOGY

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TEXAS CHILDREN'S CANCER AND HEMATOLOGY CENTERS
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Learning Objectives

1. Discuss the epidemiology, pathophysiology, risk factors, diagnosis, and general treatment approaches to common pediatric malignancies.
2. Explain the role of hematopoietic stem cell transplantation in children with hematologic or oncologic disorders.
3. Prevent and manage late treatment-related complications in survivors of childhood cancer.
4. Identify and mitigate treatment-related complications in children with cancer.
5. Propose a treatment approach for a child with blood disorders, such as hemophilia, sickle cell disease, or iron deficiency anemia.

Abbreviations in This Chapter:

ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BSA	Body surface area
COG	Children's Oncology Group
EFS	Event-free survival
GVHD	Graft-vs.-host disease
HL	Hodgkin lymphoma
HSCT	Hematopoietic stem cell transplantation
LOH	Loss of heterozygosity
NHL	Non-Hodgkin lymphoma
NUDT15	Nudix (nucleoside diphosphate linked moiety X)-type motif 15
OS	Overall survival
POGO	Pediatric Oncology Group of Ontario
SOS	Sinusoidal obstruction syndrome
TPMT	Thiopurine methyltransferase

Self-Assessment Questions

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

Questions 1–4 pertain to the following case.

M.C. is a 4-year-old girl who presents to her pediatrician with fever, pallor, and bone pain. The pediatrician does a CBC in the clinic and refers her to the cancer center at the local children's hospital. Further diagnostic analysis shows a WBC of 89×10^3 cells/mm³ with 47% blasts on peripheral blood smear. Results of a bone marrow aspirate and biopsy are conclusive for acute lymphoblastic leukemia (ALL) with no known genetic abnormalities.

1. Which statement about M.C.'s diagnosis is most accurate?
 - A. Mortality from ALL has increased substantially during the past 4 decades because of increased environmental exposures and lack of new therapeutic agents.
 - B. Mortality from ALL has decreased substantially during the past 4 decades because of new, targeted agents such as monoclonal antibodies.
 - C. Mortality from ALL has increased substantially during the past 4 decades despite a cooperative group approach to treatment and research.
 - D. Mortality from ALL has decreased substantially during the past 4 decades because of the coordinated efforts of cooperative group treatment and research.
2. Which most accurately describes the broad approach to treating M.C.'s disease?
 - A. Neoadjuvant chemotherapy, radiation, and adjuvant chemotherapy.
 - B. Induction, consolidation, and maintenance chemotherapy plus CNS prophylaxis.
 - C. Two cycles of induction chemotherapy, followed by two cycles of intensification chemotherapy.
 - D. Myeloablative chemotherapy, followed by an allogeneic stem cell transplant.
3. Which best explains why M.C. should receive CNS chemoprophylaxis?
 - A. All female patients should receive CNS chemoprophylaxis because of their increased risk of CNS-relapsed ALL compared with male patients.

- B. All children with newly diagnosed ALL should receive CNS prophylaxis to eradicate CNS disease.
 - C. CNS chemoprophylaxis enhances the efficacy of cranial irradiation and improves cognitive outcomes in children with newly diagnosed ALL.
 - D. Children with newly diagnosed ALL do not require CNS chemoprophylaxis.
4. Which best describes the corticosteroid that M.C. should receive during induction therapy and why?
- A. Dexamethasone, because this is the standard of care for children 1–10 years of age.
 - B. Hydrocortisone, because patients with newly diagnosed ALL are adrenally suppressed and require hydrocortisone supplementation.
 - C. Methylprednisolone injection, because M.C. is 4 years old and cannot swallow oral tablets.
 - D. Prednisone, because M.C. is a female and does not need the extramedullary protection offered with dexamethasone.
5. A 14-year-old male adolescent was recently given a diagnosis of stage III anaplastic large cell lymphoma (ALCL). Which is most accurate regarding the therapeutic approach for this patient's disease?
- A. Brentuximab vedotin should be added to standard conventional chemotherapy in all children with ALCL.
 - B. Crizotinib, which has significant efficacy in children and adolescents with newly diagnosed ALCL, should be given in lieu of conventional chemotherapy.
 - C. Crizotinib, together with conventional chemotherapy, can increase overall survival (OS) rates to almost 95%.
 - D. Conventional chemotherapy is the mainstay of treatment and can result in a 70%–85% OS rate.
6. A 16-year-old female adolescent was recently given a diagnosis of stage IIIB Hodgkin lymphoma (HL). She is receiving conventional chemotherapy and radiation. Which most accurately describes the outcomes she may experience after therapy?
- A. She is at risk of cardiac dysfunction, including heart failure, because of receiving doxorubicin and radiation.
 - B. She is at risk of developing pulmonary fibrosis because she received vincristine.
 - C. She is at risk of developing a secondary malignancy; however, there is currently no recommendation for long-term follow-up.
 - D. She should expect to have impaired fertility and should be advised never to become pregnant because of the risk to the fetus.
7. Which pair most closely links the toxicity with the potentially related chemotherapeutic agent?
- A. Nephrotoxicity and vincristine.
 - B. Hemorrhagic cystitis and busulfan.
 - C. Ototoxicity and doxorubicin.
 - D. Electrolyte disturbances and cisplatin.
- Questions 8–10 pertain to the following case.**
- T.H. is a 2-year-old girl with sickle cell anemia. She has been admitted to the hospital three times in the past 12 months for vaso-occlusive crises associated with sickle cell anemia. She has no history of receiving RBC transfusions, and her Hgb is at baseline concentrations. She has no known allergies. Two of T.H.'s older siblings with sickle cell anemia are adherent to their office visits and preventive treatment.
8. Which combination most accurately describes the preventive or prophylactic measures T.H. should receive?
- A. Routine childhood vaccinations, erythromycin prophylaxis, and folic acid supplementation.
 - B. Routine childhood vaccinations, penicillin prophylaxis, and folic acid supplementation.
 - C. Routine childhood vaccinations, erythromycin prophylaxis, and vitamin B₁₂ supplementation.
 - D. Routine childhood vaccinations, penicillin prophylaxis, and iron supplementation.

9. Which treatment would be considered best, given the severity of T.H.'s disease?
- A. Oral hydroxyurea therapy.
 - B. Oral deferasirox prophylaxis.
 - C. HLA-matched sibling transplantation.
 - D. Long-term RBC transfusions.
10. T.H. develops a fever with pain, swelling, and decreased range of movement in her hands. Which clinical scenario would you most likely suspect?
- A. Dactylitis; she should be treated with antibiotics that provide coverage against *Enterococcus* spp.
 - B. Dactylitis; she should be treated with antibiotics that provide coverage against *Salmonella* and *Staphylococcus* spp.
 - C. Dactylitis; she should be treated with antibiotics that provide coverage against *Streptococcus* spp.
 - D. Dactylitis; antibiotics are not clinically indicated.
11. Which is most accurate regarding iron chelation for children with sickle cell disease?
- A. Iron chelation should be considered when a patient has received 60 mL/kg of packed RBCs.
 - B. Iron chelation with deferiprone should be the first choice because deferiprone is the only oral iron chelator labeled for use in children.
 - C. Oral deferasirox can be used in children with iron overload resulting from long-term treatment with transfusions.
 - D. Deferoxamine, which is only indicated for acute iron toxicity, should not be used for oral iron chelation.
12. A 17-year-old male adolescent presents to the ED after a motor vehicle crash. He has uncontrolled bleeding from several sites of trauma (including head trauma) and cannot communicate because he was sedated and intubated in the field. His mother, who was in the accident with him, states that she knows the patient has hemophilia but cannot remember which type. You are working in the ED, and the trauma physician asks you to recommend a pharmacologic factor replacement product for this patient. Which is the most appropriate intervention for this patient at this time?
- A. Send a serum sample to the laboratory for analysis and wait for the results before selecting a blood or factor replacement product.
 - B. Suggest a recombinant factor VIII product because hemophilia A is the most common bleeding disorder in children.
 - C. Recommend recombinant factor VIIa until the laboratory can provide more information about the type of hemophilia and the presence or absence of inhibitors.
 - D. Provide a factor IX product because it will work for hemophilia A and B.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5, 1.7
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.4
3. Domain 3: Information Management, Research, and Education; Task(s): 3.2, 3.4

I. INTRODUCTION

- A. This chapter is subdivided into three main sections:
1. Supportive care in pediatric oncology
 2. Clinical review of pediatric malignancies
 3. Clinical review of hematologic disease states in children
- B. The general pediatric pharmacist is encouraged to be proficient in the following areas of study:
1. Classic or characteristic antineoplastic-induced adverse events
 2. Chemotherapy- or antineoplastic-induced nausea and vomiting
 3. Tumor lysis syndrome
 4. Febrile neutropenia
 5. Acute lymphoblastic leukemia (ALL)
 6. Sickle cell disease
 7. Iron deficiency anemia
 8. Hemophilia
- C. Chemotherapy Dosing Approaches
1. Chemotherapy can be dosed by patient weight (in kilograms), by body surface area (BSA; in square meters), or in fixed doses. Fixed, age-based doses are also used for intrathecal, intra-arterial, intravenous, and intracerebroventricular doses of chemotherapy.
 2. The Mosteller method is most commonly used to calculate BSA in pediatric oncology:
- $$\text{BSA (m}^2\text{)} = \sqrt{[(\text{height} \times \text{weight}) \div 3600]}$$
- where height is in centimeters and weight is in kilograms.
- D. Infants (weight 10–12 kg, in most cases) will have a disproportionately larger BSA relative to body weight, resulting in higher total drug exposure and excess toxicity when dosed per square meter versus kilogram.
1. Doses for infants (or weight less than 10–12 kg) are commonly converted from milligram per square meter to milligram per kilogram using a “factor” of 30.
 - a. This conversion is based on the assumption that a patient with a BSA of about 1 m² will typically weigh around 30 kg.
 - b. Example: Doxorubicin 30 mg/m² = doxorubicin 1 mg/kg.
 2. Other approaches have recently been explored, including the use of predefined dosing tables, which provide a dose that falls between the mg/m² and mg/kg doses.

Patient Case

1. You are working with the interdisciplinary medical team on the chemotherapy orders for an 8-month-old patient (weight 7 kg) with a newly diagnosed stage I favorable-histology Wilms tumor (tumor weight 600 g, no loss of heterozygosity [LOH] at 1p and 16q). The team would like to initiate therapy with a two-drug regimen, EE4A, containing vincristine and dactinomycin. Which pair of doses is most appropriate?
 - A. Vincristine 0.05 mg/kg; dactinomycin 0.045 mg/kg.
 - B. Vincristine 0.05 mg/kg; dactinomycin 2.5 mg.
 - C. Vincristine 1.5 mg/m²; dactinomycin 0.045 mg/kg.
 - D. Vincristine 2.5 mg; dactinomycin 0.045 mg/kg.

II. SUPPORTIVE CARE IN PEDIATRIC ONCOLOGY

A. Antineoplastic-Induced Adverse Events

1. Antineoplastics have long been associated with several adverse events in both the acute and late settings. The following list describes important adverse events associated with antineoplastics in children and adolescents with cancer. Note that not all adverse events are described; rather, hallmark and significant events are described.
2. Cardiotoxicity
 - a. Cardiotoxicity is perhaps one of the best-known adverse events and late effects of therapy in children and adolescents with cancer.
 - b. The risk of serious cardiotoxic events increases with increasing doses of anthracyclines (often greater than a lifetime cumulative dose of 300 mg/m² of doxorubicin equivalents), and they can occur after receipt of any dose. Other risk factors include high single doses or dose intensity of the anthracycline, longer follow-up time after the anthracycline, mediastinal radiation, female sex, tumor type (e.g., rhabdomyosarcoma, Wilms tumor), and receipt of other cardiotoxic agents.
 - c. Acute cardiac effects of the anthracyclines may include transient ECG changes; late effects can include left ventricular dysfunction and cardiac failure, potentially necessitating heart transplantation.
 - d. Studies to date have shown no benefit of continuous infusions over bolus infusions of anthracyclines in children with cancer.
 - e. Adding dexrazoxane to anthracycline-containing regimens decreases the risk of cardiotoxicity and does not appear to compromise survival in pediatric patients. Many contemporary protocols include dexrazoxane with up-front anthracyclines – doxorubicin, mitoxantrone, and daunorubicin.
3. Electrolyte disturbances
 - a. Commonly experienced as hyperphosphatemia, hyperkalemia, and hypocalcemia in children with tumor lysis syndrome
 - b. May present as electrolyte wasting after receipt of cisplatin (hypokalemia, hyponatremia, hypomagnesemia) or ifosfamide (Fanconi renal wasting with hyponatremia, hypophosphatemia, hypokalemia, glycosuria, and metabolic acidosis)
 - c. Sodium disturbances, such as syndrome of inappropriate antidiuretic hormone, may rarely be experienced in patients receiving vincristine or cyclophosphamide.
4. Hemorrhagic cystitis
 - a. Hemorrhagic cystitis is an established adverse event associated with acrolein and a toxic metabolite of both cyclophosphamide and ifosfamide. Incidence varies by agent and dose, with the highest risk associated with ifosfamide over cyclophosphamide and an incidence of about 44% and 15%, respectively, without mesna. Risk factors include higher single doses of cyclophosphamide or ifosfamide and prior receipt of busulfan.
 - b. Hemorrhagic cystitis can be prevented or minimized with appropriate hydration and the use of mesna. For prophylaxis, mesna is dosed at 60%–100% per equivalent milligram (weight/weight) of the cyclophosphamide or ifosfamide dose. Mesna should be used in all patients receiving any dose of ifosfamide. Use of mesna as prophylaxis with higher doses of cyclophosphamide is also recommended, though no clear breakpoint for use has been described. Clinicians generally recommend mesna for cyclophosphamide doses greater than 1000–1200 mg/m². Mesna is provided as a continuous infusion (through at least 12 hours after the discontinuation of cyclophosphamide or ifosfamide) or is fractionated into three to five doses at hours 0, 4, and 8 or hours 0, 3, 6, 9, and 12. Though generally administered intravenously, oral mesna may be an option for select patients. Of note, mesna is a ketone that can result in the detection of ketones on urinalysis.
 - c. Mesna and increased hydration can also be used in the treatment of hemorrhagic cystitis. For treatment, mesna is administered as either a continuous infusion or at a higher dose, when possible.

Patient Case

2. Your patient will receive ifosfamide dosed at 1800 mg/m^2 per day for 5 consecutive days. Which is most appropriate for preventing hemorrhagic cystitis?
- A. Hyperhydration alone is sufficient for this dose of ifosfamide.
 - B. Administer a mesna continuous infusion starting at the end of the fifth day of ifosfamide.
 - C. Administer hydration together with mesna 360 mg/m^2 intravenously at hours 0, 4, and 8, respective to the start of the ifosfamide dose.
 - D. Administer mesna 240 mg/m^2 intravenously at hours 0, 3, 6, 9, and 12, respective to the start of the ifosfamide dose.

5. Nephrotoxicity

- a. Nephrotoxicity has been associated with several antineoplastic agents, perhaps most notably cisplatin and methotrexate.
- b. Estimated glomerular filtration may not correlate closely with actual glomerular filtration in children with cancer.
- c. Children receiving nephrotoxic chemotherapy and supportive care agents should be monitored at the start of, throughout, and after therapy to assess for changes in renal function.
- d. Hyperhydration is a key element to prevent tubular damage from agents such as cisplatin and high-dose methotrexate.

6. Osteonecrosis

- a. Severe osteonecrosis may necessitate steroid discontinuation, which may in turn decrease survival.
- b. It is generally accepted that children with ALL/lymphoblastic lymphoma who are 10 years and older should receive prednisone as the steroid of choice because dexamethasone is associated with an increased risk of osteonecrosis in adolescent patients.
- c. Discontinuous dexamethasone should be used in the delayed intensification phase of treatment for adolescents and young adults with ALL/lymphoblastic lymphoma because of the increased risk of osteonecrosis.
- d. The risk of osteonecrosis varies with race and ethnicity, with Hispanic children having a lower risk than non-Hispanic children.

7. Ototoxicity

- a. High-frequency hearing loss and tinnitus are well-known adverse events of therapy with cisplatin (primarily) and carboplatin (to a lesser degree) in children and adolescents. Both adverse events are associated with increasing cumulative doses and may be irreversible after therapy is discontinued.
- b. When possible, coadministration of other ototoxic agents should be avoided (e.g., aminoglycosides).
- c. All children who will receive a platinum agent should receive audiometric testing before, during, and after therapy. Some protocols may include recommendations to change from cisplatin to carboplatin or to a different, non-platinum chemotherapy on the basis of audiometric results throughout therapy.
- d. The Children's Oncology Group (COG) has endorsed the clinical practice guideline on the prevention of cisplatin-induced ototoxicity in children and adolescents with cancer as developed by the Pediatric Oncology Group of Ontario (POGO). This guideline recommends the following:
 - i. Use of sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with nonmetastatic hepatoblastoma
 - ii. Consideration of sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children and adolescents with nonmetastatic cancers other than hepatoblastoma

- e. The COG guideline recommends **against** the following measures for the prevention of cisplatin-induced ototoxicity in children and adolescents:
 - i. Altering the cisplatin duration to reduce ototoxicity
 - ii. Intratympanic middle ear therapy
 - iii. Sodium diethyldithiocarbamate
 - iv. Amifostine
 - v. Use of sodium thiosulfate in children and adolescents with metastatic cancers
- 8. Peripheral neuropathy
 - a. Peripheral neuropathy is a well-known risk of vinca alkaloid (e.g., vincristine) and platinum (e.g., cisplatin) therapy.
 - b. For vincristine, the risk of peripheral neuropathy increases with cumulative doses, though no hard maximum cumulative dose has been established (single doses of vincristine are typically capped at 2 mg each). Neuropathy is commonly graded according to the Balis scale, with interventions and dose modifications based on the grade or severity.
- 9. Sinusoidal obstruction syndrome (SOS)
 - a. SOS is a severe and potentially fatal syndrome that occurs after hepatic injury. SOS may present after hematopoietic stem cell transplantation (HSCT) or the receipt of specific chemotherapeutics. Potentially causative agents include alkylating agents (e.g., busulfan, cyclophosphamide), platinum, dactinomycin, thiopurines (mercaptopurine and thioguanine), gemtuzumab ozogamicin, and inotuzumab ozogamicin. SOS may manifest as abdominal pain, edema, weight gain, or jaundice. Patients may also develop portal hypertension and significant elevations in serum transaminases.
 - b. The three historically recognized diagnostic criteria are the revised Seattle criteria, the Baltimore criteria, and the Ponte di Legno consensus definition. More recently, the European Society for Blood and Marrow Transplantation (EBMT) proposed a new pediatric-specific diagnostic criteria and severity scale. These criteria evaluate clinical parameters such as serum bilirubin, weight gain, hepatomegaly, ascites, right upper quadrant pain, respiratory or renal failure, consumptive thrombocytopenia, and hepatic encephalopathy.
 - c. In some centers, ursodiol or low-dose heparin has been used for the prophylaxis of SOS in selected patients, though its clinical benefit is limited. Some centers have used defibrotide as prophylaxis, despite lack of benefit in a Phase III trial.
 - d. Treatment of SOS is primarily symptomatic. Defibrotide was recently approved for SOS treatment in children after HSCT. The exact mechanism of action of defibrotide is not well understood. However, in short, defibrotide is believed to reduce endothelial cell activation and protect endothelial cells from further damage. Many processes for this have been proposed, including hydrolysis of fibrin clots through enhanced activity of plasmin, increased expression of tissue plasminogen activator and thrombomodulin, and decreased expression of von Willebrand factor.
 - e. Defibrotide was approved for SOS treatment in patients who also have renal or pulmonary dysfunction after HSCT on the basis of compassionate use and retrospective data (i.e., no phase III randomized studies).
- 10. In addition to the aforementioned adverse events, the clinician should be aware of clinical nuances such as the need for seizure prophylaxis with busulfan, the potential risk of developing pulmonary fibrosis after bleomycin therapy, and the potential risk of developing secondary malignancies (e.g., from radiation, alkylating agents, and etoposide), as well as the counseling points regarding fertility during and after therapy and the treatment approaches to vesicant extravasation.
- 11. Additional general supportive care issues are described separately in the subsections that follow.

B. Chemotherapy-Induced Nausea and Vomiting

1. Antineoplastic- or chemotherapy-induced nausea and vomiting are associated with negative consequences in children and adolescents, including reduced quality of life, dehydration, and anxiety or concern about the receipt of chemotherapy.
2. POGO published an evidence-based guideline (and recently a partial update to the guideline) for the approach to preventing chemotherapy-associated acute nausea and vomiting in children with cancer. The group's general recommendations are as follows and are based on the emetogenicity of the treatment regimen:
 - a. Minimal emetogenic risk: No routine prophylaxis
 - b. Low emetogenic risk: Single-agent ondansetron or granisetron
 - c. Moderate emetogenic risk:
 - i. If corticosteroids are permitted: Dexamethasone plus ondansetron or granisetron or palonosetron
 - ii. If corticosteroids are contraindicated
 - (a) Age younger than 6 months: Palonosetron
 - (b) Age 6 months and older: Aprepitant plus ondansetron or granisetron or palonosetron. Aprepitant should be held or avoided if the patient is receiving an antineoplastic agent known to interact with aprepitant (e.g., agents known to interact through CYP3A4, such as dabrafenib, ifosfamide).
 - d. High emetogenic risk
 - i. If corticosteroids are permitted
 - (a) Age younger than 6 months: Dexamethasone plus ondansetron or granisetron or palonosetron
 - (b) Age 6 months and older: Aprepitant plus dexamethasone plus ondansetron or granisetron or palonosetron. Aprepitant should be held or avoided if the patient is receiving an antineoplastic agent known to interact with aprepitant. The steroid dose should be reduced (according to labeling) when given with aprepitant.
 - ii. If corticosteroids are contraindicated
 - (a) Age younger than 6 months: Palonosetron
 - (b) Age 6 months and older: Aprepitant plus palonosetron. Aprepitant should be held or avoided if the patient is receiving an antineoplastic agent known to interact with aprepitant.
 - e. The POGO publication recognizes several gaps in the data for preventing and treating chemotherapy-induced nausea and vomiting, including domains such as the appropriate dosing approach for selected agents (i.e., dexamethasone, palonosetron), the safety and adverse effect profile of corticosteroids in children when used as antiemetics, the efficacy of nonpharmacologic approaches and adjunctive agents, and the health-related outcomes associated with the guideline recommendations.
 - f. POGO has also published two additional guidelines as follows (readers are encouraged to review the guidelines as referenced for additional information):
 - i. Guideline for the Prevention and Treatment of Anticipatory Nausea and Vomiting Due to Chemotherapy in Pediatric Cancer Patients
 - ii. Guideline for the Treatment of Breakthrough and the Prevention of Refractory Chemotherapy-Induced Nausea and Vomiting in Children with Cancer
 - g. Readers are also encouraged to familiarize themselves with known interactions with aprepitant (see referenced publication).
 - h. Several other agents have historically been used for preventing and treating acute, breakthrough, refractory, and anticipatory emesis with varying degrees of efficacy. Practitioners treating children with cancer should be familiar with the safety and efficacy of a variety of other agents that may be effective antiemetics, such as olanzapine, chlorpromazine, metoclopramide, and diphenhydramine.

C. Infectious Risks and Complications

1. *Pneumocystis* prophylaxis

- a. Children and adolescents receiving myelotoxic chemotherapy are at an increased risk of neutropenia, lymphopenia, and subsequent infectious complications. These patients should receive prophylaxis against *Pneumocystis jiroveci* from the start of therapy through about 6 months after therapy.
- b. The preferred agent for prophylaxis in most patients is sulfamethoxazole/trimethoprim. However, some patients may be ineligible for the receipt of sulfamethoxazole/trimethoprim. Patients with a sulfa allergy may require an alternative agent such as pentamidine or atovaquone. Those with pre-existing prolongation of the QT interval may be limited to dapsone or atovaquone. Patients with a history of severe pancreatitis may require dapsone or atovaquone. Sulfamethoxazole/trimethoprim should be avoided in neonates because of the risk of kernicterus. Many clinical trials recommend that patients receiving high-dose intravenous methotrexate have a separation of about 24 hours between methotrexate clearance and sulfamethoxazole/trimethoprim.

2. Antibacterial prophylaxis

- a. COG has endorsed the Guideline for Antibacterial Prophylaxis Administration in Pediatric Cancer and Hematopoietic Stem Cell Transplantation. This guideline was originally created by POGO.
- b. The guideline recommends to **consider** systemic antibacterial prophylaxis in children with acute myeloid leukemia (AML) and relapsed ALL receiving intensive chemotherapy expected to result in severe neutropenia (absolute neutrophil count less than 500 cells/mm³) for at least 7 days. The primary agent recommended is levofloxacin, and only during periods of severe neutropenia, which may last for days or weeks.
- c. The guideline recommends **against** routine systemic prophylaxis in children receiving induction chemotherapy for newly diagnosed ALL, those undergoing autologous or allogeneic HSCT, and those whose therapy is not expected to result in severe neutropenia for at least 7 days (i.e., those patients with a shorter duration of neutropenia).

3. Antifungal prophylaxis

- a. COG has endorsed the Clinical Practice Guideline for Systemic Antifungal Prophylaxis in Pediatric Patients with Cancer and Hematopoietic Stem-Cell Transplantation Recipients as created by POGO.
- b. Prophylaxis is recommended in the following populations: patients with ALL at high risk of invasive fungal disease, patients with AML, and patients undergoing an allogeneic HSCT. In these patients, mold-active agents should be used according to local epidemiology, adverse effect profile, potential for drug interactions, cost, and availability. Example agents include an echinocandin, voriconazole, and itraconazole. In patients 13 years and older, posaconazole can also be used.
- c. Prophylaxis is not routinely recommended in patients with lymphomas or solid tumors or in those receiving an autologous HSCT. American Society for Transplantation and Cellular Therapy guidelines recommend fluconazole prophylaxis in patients with an underlying malignant diagnosis and anticipated duration of neutropenia of at least 7 days.

Patient Case

3. The oncology fellows at your institution have asked for a review of the appropriate use of antifungal prophylaxis in children with cancer or those receiving HSCT. Which best represents a guideline-supported prophylactic recommendation for children receiving an allogeneic HSCT?
 - A. Prophylaxis is not recommended.
 - B. Administer fluconazole.
 - C. Administer caspofungin.
 - D. Administer amphotericin B.

4. Febrile neutropenia

- a. Children and adolescents who develop a fever while having neutropenia (absolute neutrophil count less than 500 cells/mm³) require close evaluation for various infectious causes. Each institution should develop a guideline for treating febrile neutropenia.
- b. The Infectious Diseases Society of America Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer includes several specific recommendations. Although most of the guideline's supporting evidence is from adult trials, readers are still encouraged to review this guideline as well as the organism-specific guidelines available on the Infectious Diseases Society of America website (www.idsociety.org). Salient parts of the guideline include the following:
 - i. Removal of the central line should be considered for certain infectious causes and conditions.
 - ii. High-risk patients should receive intravenous empiric antibiotic monotherapy with an antipseudomonal β -lactam (e.g., cefepime, a carbapenem [meropenem or imipenem/cilastatin], piperacillin/tazobactam). Vancomycin is not routinely recommended as a standard part of the initial antibiotic regimen for fever and neutropenia but should be considered for specific clinical indications such as suspected catheter-related infection, skin and soft tissue infection, pneumonia, hemodynamic instability, or at centers with a high rate of beta lactam-resistant gram-positive organism.
- c. The International Pediatric Fever and Neutropenia Guideline Panel published a guideline for the initial and ongoing treatment of children with cancer or those undergoing HSCT in 2012, with a 2017 update. Readers are encouraged to review this guideline in detail. The following algorithm summarizes the recommendations (Figure 1):

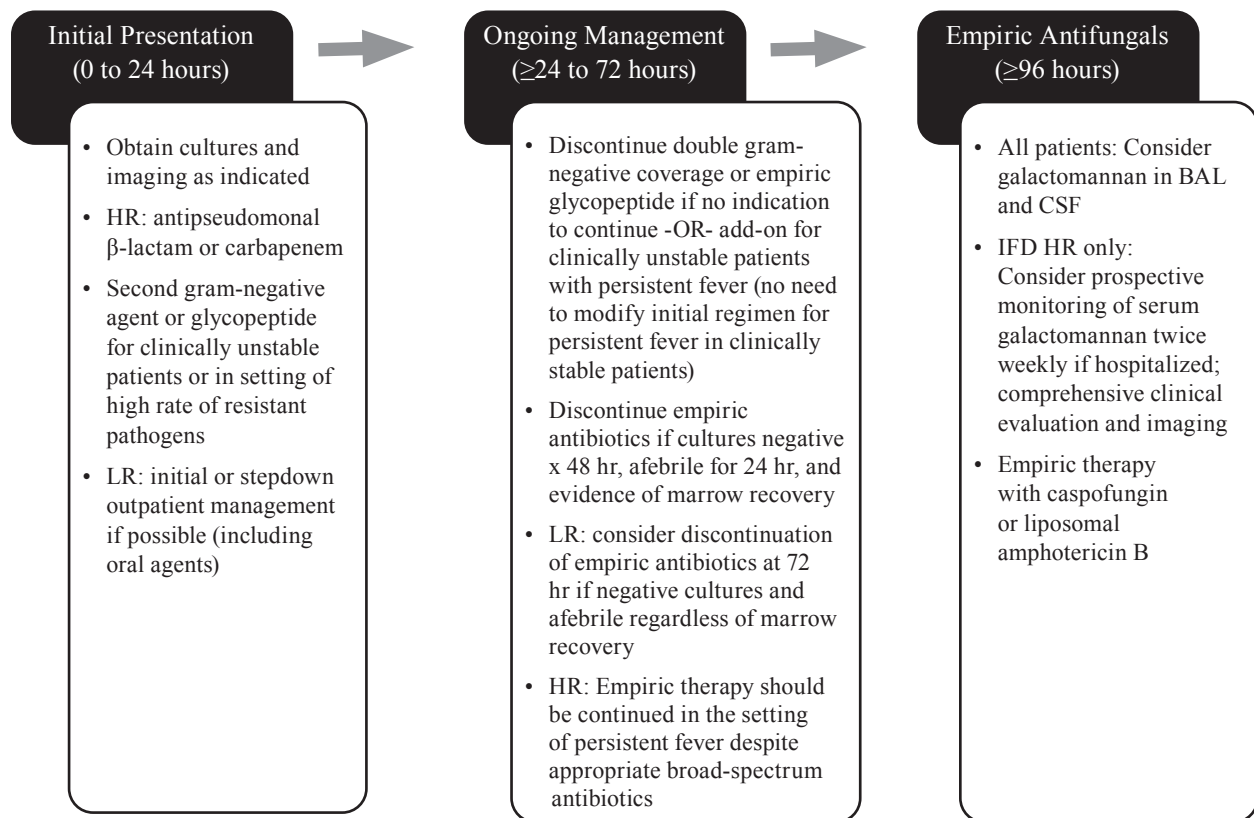


Figure 1. Pediatric fever and neutropenia management algorithm.

BAL = bronchoalveolar lavage; HR = high risk; IFD = invasive fungal disease; LR = low risk.

D. Mucositis

1. All patients are encouraged to follow good oral hygiene.
2. The POGO Mucositis Prevention Guideline Development Group published evidence-based recommendations for preventing oral and oropharyngeal mucositis in children receiving treatment for cancer or undergoing HSCT.
 - a. The recommendations state that patients should routinely be assessed for the presence and severity of oral mucositis. Validated assessment tools should be considered, such as the ChIMES (Children's International Mucositis Evaluation Scale), the Oral Assessment Guide, the Oral Mucositis Daily Questionnaire, or the Oral Mucositis Assessment Scale.
 - b. The POGO guideline includes recommendations for the use of preemptive cryotherapy or LLLT (low-level light therapy) in cooperative children receiving chemotherapy or HSCT conditioning regimens that are associated with a high rate of mucositis.
 - c. The guideline also suggests that the keratinocyte growth factor (palifermin) be considered in children receiving HSCT conditioning with regimens associated with a high rate of severe mucositis. However, the panel notes that this recommendation is based on adult data; therefore, the guideline encourages additional clinical investigation into this agent to clarify the optimal dose, assess the potential short- and long-term risks and toxicities, and evaluate the long-term follow-up in children.
3. Treatment of mucositis in children is supportive and aims to relieve symptoms. Supportive care should include oral or intravenous pain management (including patient- or provider-controlled analgesia, when necessary) and intravenous hydration or parenteral nutrition, or both, when appropriate. Resolution of mucositis typically follows marrow recovery.

E. Pain

1. Acute or persistent (chronic) pain is a significant problem for children and adolescents with hematologic and oncologic disorders. Examples of pain-associated conditions include the following:
 - a. Acute pain
 - i. Direct tumor-related pain as a result of the compression of nervous tissue or the distension, inflammation, pressure, or obstruction of other tissues
 - ii. Procedural pain, such as bone marrow aspiration or biopsy, lumbar puncture, or postsurgical pain
 - iii. Mucositis (see the Mucositis section)
 - iv. Spinal cord compression
 - v. Vaso-occlusive crises in children with sickle cell disease
 - b. Persistent or chronic pain
 - i. Amputation-related pain, including phantom limb pain
 - ii. Bone or joint pain caused by bone or bone marrow involvement of disease
 - iii. Neuropathic pain, such as that caused by chemotherapy or invasion of the CNS
 - iv. Osteonecrosis as a result of high-dose or prolonged corticosteroid exposure
 - v. Avascular necrosis as a result of poor oxygenation caused by repeated sickle cell crises or corticosteroid exposure
2. Because of pharmacologic changes, experiences throughout development, and variability in the cause of pain, it is difficult to create a simple approach to the management of chronic pain in children. Instead, an approach tailored by experienced professionals trained in pain management should be made available.
3. Assessment of pain must be appropriate for the patient's age, developmental stage, and clinical condition. Vital signs such as heart rate and blood pressure can be used for all patients, but their use is limited by other disease states and therapeutic interventions, which can result in various physiologic alterations.

4. A variety of pain scales have been studied and evaluated. The pain intensity scales recommended by the Pediatric Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (Ped-IMMPACT) and the Society of Pediatric Psychology Pain Assessment Task Force (SPP-ATF) are as follows:
 - a. Faces Pain Scale–Revised for children 4–12 years of age
 - b. Pieces of the Hurt/Poker Chip Tool for children 3–12 years of age
 - c. Visual analog scale for children 8 years and older
 - d. Oucher photographic and 0–10 numeric rating scales for children 3–12 years and older than 8 years, respectively
5. Other pain intensity scales that have been used in infants, children, and adolescents include the following:
 - a. Neonatal behavioral and physiologic scales for premature to full-term infants
 - i. CRIES (crying, requires oxygen, increased vital signs, expression, sleepless) instrument
 - ii. Neonatal Facial Coding System (NFCS)
 - iii. Neonatal Infant Pain Scale (NIPS)
 - iv. Premature Infant Pain Profile (PIPP)
 - b. FLACC (face, legs, activity, cry, consolability) scale for children 2 months to 7 years of age
 - c. Wong-Baker Faces scale for children 3 years and older
6. Some of the aforementioned scales and tools may not be useful for children with cognitive impairment. A scale such as the Non-communicating Children's Pain Checklist–Postoperative Version (NCCPC-PV) may be more appropriate.
7. According to the WHO, appropriate treatment of persisting pain in children with medical illness should involve the following four approaches:
 - a. Use of a “two-step” strategy
 - i. Step 1: Treatment of mild pain with acetaminophen or ibuprofen (if clinically appropriate)
 - ii. Step 2: Treatment of moderate to severe pain with a strong opioid such as morphine
 - iii. Of note, the former “three-step” approach was recently abandoned because of mounting evidence that codeine, a weak opioid previously recommended in the former approach, has significant safety and efficacy concerns.
 - (a) The FDA has released several safety warnings and has required a revision to the product labeling to inform health care professionals, patients, and caregivers about the risks of codeine use in children and breastfeeding women.
 - (b) The FDA has also recently released a statement about the rare, but serious risk of difficult or slowed breathing associated with the use of tramadol in children. Tramadol has not sufficiently been studied in children and is not licensed in several countries for the treatment of pain in children.
 - (c) Both of these agents are metabolized at least in part by CYP2D6. CYP2D6 is a highly polymorphic enzyme, producing a wide variety of effects depending on the host metabolizer status. Patients who are ultrarapid metabolizers of CYP2D6 will experience enhanced metabolism of codeine to morphine and thus increased or toxic effects at package-labeled doses of codeine. Patients with normal metabolizer status can safely receive codeine (or other agents metabolized by this pathway) and achieve appropriate analgesia.
 - b. Dosing of medications at regular intervals
 - i. In most cases, a regular “around-the-clock” dosing approach should be used, with the addition of rescue doses for intermittent or breakthrough pain.
 - ii. In some circumstances, as-needed doses may be appropriate, instead of scheduled doses, when the pain is truly unpredictable.
 - c. Use of an appropriate administration route
 - i. The oral route of administration should be used, when possible, because of convenience and cost.

- ii. Intramuscular dosing should be avoided. Rectal administration can be associated with variability in bioavailability and is considered inappropriate for children with neutropenia, thrombocytopenia, or an otherwise impaired immune system.
 - d. Adaptation of therapy to the needs of the individual
 - i. Pain management should be carefully tailored and titrated to the needs of the child. There is no “one-size-fits-all” approach and no maximum dose for opioids when treating the child with persisting pain.
 - ii. Although a routine rotation of opioids is not recommended, an opioid switch or opioid rotation may be appropriate for a child who has not responded to a carefully considered dose of a strong opioid.
 - 8. Adjuvant agents have been used in children and adults for the management of neuropathic pain (i.e., tricyclic antidepressants, selective serotonin reuptake inhibitors, ketamine, local anesthetics, lidocaine patch, and anticonvulsants such as gabapentin and carbamazepine). However, the WHO states that because of limitations in the available evidence, it is not possible to recommend for or against these agents.
 - 9. Adjuvant pain management approaches may also include nonpharmacologic techniques (e.g., heat, ice, guided imagery).
- F. Survivorship Issues
- 1. About 1 in 530 adults (20–39 years of age) are childhood cancer survivors. An estimated 420,000 survivors of childhood and adolescent cancer are living in the United States.
 - 2. Survivors of childhood cancer may have growth deficiencies, neurocognitive deficits, cardiotoxicity (including heart failure), ototoxicity, impaired renal function, neuropathies, pulmonary fibrosis, endocrinopathies, metabolic syndromes, impaired fertility, complications during pregnancy, and an increased rate of secondary cancers. All survivors of cancer should be monitored in a long-term follow-up setting by providers with expertise in monitoring and treating these complications.
 - 3. COG has created the Long-term Follow-up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers to provide health care professionals with a resource regarding the appropriate ongoing care and needs of survivors of childhood and adolescent cancers. These guidelines are comprehensive, specific, and freely accessible at www.survivorshipguidelines.org/.
- G. Tumor Lysis Syndrome
- 1. Tumor lysis syndrome occurs as a result of the massive release of intracellular contents after tumor cell death. Tumor lysis syndrome can occur spontaneously before initial chemotherapy or shortly after initiating therapy. Tumor lysis syndrome is more common with aggressive hematologic or oncologic disease states, such as newly diagnosed acute leukemias or Burkitt lymphoma, but also occurs rarely with some solid tumors, such as alveolar rhabdomyosarcoma. Tumor lysis can result in hyperuricemia, hyperkalemia, hyperphosphatemia, or hypocalcemia.
 - 2. Tumor lysis syndrome is managed with either primary prophylactic measures or treatment, depending on the patient’s clinical presentation. Clinical pearls for managing specific aberrations are as follows:
 - a. Hyperuricemia
 - i. Use of sodium bicarbonate to facilitate alkalinization of urine and improved uric acid elimination has generally fallen out of favor because of the risk of calcium phosphate precipitation when rasburicase is used to treat hyperuricemia.
 - ii. In many patients (as described later), allopurinol can play a role in preventing hyperuricemia. Allopurinol is a xanthine oxidase inhibitor that prevents the conversion of hypoxanthine to xanthine and xanthine to uric acid; it does not eliminate existing uric acid.
 - iii. Rasburicase may be warranted in high-risk patients. Rasburicase catalyzes the conversion of uric acid to allantoin, a more soluble renally eliminated product. Rasburicase should be avoided in patients with a known or potential history of glucose-6-phosphate dehydrogenase deficiency because of the risk of hemolytic anemia after administration.

- b. Hyperkalemia
 - i. Elevated potassium concentrations may warrant cardiac rhythm monitoring with ECG and renal or cardiac expert consultation.
 - ii. Hyperkalemia can be prevented and managed through restriction or elimination of potassium in intravenous fluids. Although intravenous calcium is often recommended for symptomatic hyperkalemia to stabilize the myocardium, its use should be carefully considered, weighing the risk of potential calcium phosphate precipitation, which can induce or worsen existing renal dysfunction.
 - c. Hyperphosphatemia
 - i. Prevention and management of hyperphosphatemia can include a phosphorus-restricted diet, use of an oral phosphate binder such as sevelamer, or both.
 - ii. Calcium should not be used to reduce phosphate concentrations because of the risk of calcium phosphate precipitation in the renal tubules.
 - d. Hypocalcemia
 - i. The primary treatment approach for hypocalcemia in the setting of tumor lysis syndrome is often correction of elevated serum phosphorus concentrations.
 - ii. Correction of hypocalcemia should be approached with caution to minimize the risk of calcium phosphate precipitation and the potential for impaired renal function. Calcium replacement should be provided for symptomatic hypocalcemia.
3. All patients should be monitored closely, with laboratory analysis of WBC, LDH, SCr, urinary output, serum electrolytes (most importantly, potassium, phosphate, magnesium, and calcium), and serum uric acid. Other laboratory tests may be required, depending on the patient's clinical presentation.
4. Several guidelines have been published providing recommendations for the evaluation, prophylaxis, and treatment of tumor lysis syndrome. These guidelines provide specific diagnosis- and clinically based recommendations. In each guideline, patients are usually subcategorized into groups with a low, intermediate, or high risk of developing tumor lysis syndrome. Pediatric-specific examples are included in the lists that follow:
- a. Low risk
 - i. Diagnoses:
 - (a) Most solid tumors
 - (b) Indolent non-Hodgkin lymphoma (NHL)
 - (c) Hodgkin lymphoma (HL)
 - (d) AML with WBC less than 25×10^3 cells/mm³ and LDH less than 2 times the upper limit of normal (ULN)
 - ii. Prophylaxis: Hydration with or without allopurinol
 - b. Intermediate risk
 - i. Diagnoses:
 - (a) Selected solid tumors with bulky or advanced-stage disease (e.g., neuroblastoma, germ cell tumors)
 - (b) ALL with WBC less than 100×10^3 cells/mm³ and LDH less than 2 times the ULN
 - (c) AML with WBC $25\text{--}100 \times 10^3$ cells/mm³ or AML with WBC less than 25×10^3 cells/mm³ and LDH 2 times or more the ULN
 - (d) Anaplastic large cell lymphoma (ALCL) (stage III or IV only)
 - (e) Intermediate-grade NHL with LDH less than 2 times the ULN (stage III or IV only)
 - (f) Burkitt lymphoma with LDH less than 2 times the ULN
 - (g) Lymphoblastic lymphoma, stage I or II, with LDH less than 2 times the ULN
 - ii. Prophylaxis: Hydration plus allopurinol

- c. High risk
 - i. Diagnoses:
 - (a) ALL with WBC of 100×10^3 cells/mm³ or greater, LDH 2 times or more the ULN, or both
 - (b) AML with WBC of 100×10^3 cells/mm³ or greater
 - (c) Burkitt lymphoma (stage III or IV), LDH 2 times or more the ULN, or both
 - (d) Lymphoblastic lymphoma (stage III or IV), LDH 2 times or more the ULN, or both
 - (e) Any intermediate-risk patient with renal dysfunction or involvement
 - (f) Any intermediate-risk patient with serum uric acid, potassium, or phosphate above the ULN
 - ii. Prophylaxis: Hydration plus rasburicase (or allopurinol in patients with glucose-6-phosphate dehydrogenase deficiency)

III. INTRODUCTION TO PEDIATRIC ONCOLOGY

- A. Epidemiology
 - 1. Cancer is the second leading cause of death in children 5–14 years of age.
 - 2. About 1 in 285 children will receive a diagnosis of cancer, representing around 11,000 new cases annually in the United States.
 - 3. Long-term survival is around 90% overall, with about 1200 deaths each year in children and adolescents between birth and 14 years of age.
 - 4. The most common malignancies in children are leukemias (26%), CNS tumors (18%), and lymphomas (14%).
- B. Cooperative Group Research
 - 1. Currently COG, a National Cancer Institute-supported cooperative group with a worldwide presence concentrated throughout the United States, Canada, New Zealand, and Australia, is the largest cooperative research group in pediatric oncology.
 - 2. From 1975 to 2010, mortality for children and adolescents with cancer declined by an average of 2.1% annually, producing an overall decline greater than 50%. The greatest improvements were in ALL, NHL, and HL.

IV. ACUTE LYMPHOBLASTIC LEUKEMIA

- A. Epidemiology
 - 1. ALL is the most common malignancy in children between birth and 14 years of age, representing 26% of all new diagnoses and an estimated 3100 new cases in children and adolescents each year.
 - 2. ALL is the leading cause of childhood cancer death, despite substantial improvements in treatment, because of the many patients with the disease and the poor prognosis associated with relapsed disease.
 - 3. The peak incidence of disease is in children 2–5 years of age. The incidence of ALL in children 2–3 years of age is about 4-fold higher than in infants and older children.
- B. Pathophysiology and Risk Factors
 - 1. ALL is characterized by abnormal proliferation of precursor B- or T-cell lymphocytes. Genetic aberrations contribute to the development of abnormal clones and the various subtypes.
 - 2. A variety of heritable risk factors have been associated with an increased risk of ALL, including Down syndrome (10- to 20-fold increased risk), Bloom syndrome, Fanconi anemia, Nijmegen breakage syndrome, and immunodeficiency syndromes.

3. Limited data analyses suggest that maternal exposure to paint, parental cigarette smoking, and higher birth weight are associated with an increased risk of childhood ALL.
4. Prognostic features include the following:
 - a. National Cancer Institute risk classification for B-ALL
 - i. Standard risk: WBC count less than 50,000/ μ L and 1 year of age to younger than 10 years of age.
 - ii. High risk: WBC count 50,000/ μ L or greater and/or age 10 years or older.
 - b. The presence of extramedullary disease (i.e., CNS) or testicular involvement is considered a poor risk factor.
 - c. Steroid pretreatment
 - d. Response to induction therapy (poor response: minimal residual disease of 0.01% or greater after induction)
 - e. Known genetic alterations
 - i. Favorable: *ETV6-RUNX1*, hyperdiploidy with favorable chromosome trisomies (i.e., trisomy 4 and 10)
 - ii. Unfavorable: Histone-lysine-N-methyltransferase 2A (*KMT2A*) rearrangements, hypodiploidy, Philadelphia chromosome (also known as the translocation of chromosomes 9 and 22, t(9;22), Philadelphia chromosome positive [Ph⁺], or *BCR/ABL*), Philadelphia-like rearrangements (ABL-class fusions other than BCR-ABL, CRLF2 or other JAK-STAT activating mutations), and intrachromosomal amplification of chromosome 21 (iAMP21)

C. Diagnosis

1. Typically, patients with ALL present with several nonspecific signs and symptoms (i.e., fever, bleeding, bone pain, lymphadenopathy, hepatosplenomegaly, and abnormal hematopoiesis) that mimic those of other childhood illnesses.
2. Diagnosis is based on a pathologic evaluation of the blood and bone marrow for the presence of blasts and cytogenetic abnormalities before treatment.
3. Staging is performed at diagnosis and throughout therapy according to treatment response.
4. Cytogenetic and minimal residual disease evaluations are critical in ascertaining risk status and response to therapy.

D. Treatment and Outcomes

1. Treatment involves several phases of therapy with varying degrees of intensity:
 - a. Induction (4–6 weeks)
 - i. Standard-risk patients receive a three-drug induction (vincristine, dexamethasone, and pegaspargase) plus CNS-directed therapy.
 - ii. High-risk patients receive a four-drug induction, which adds daunorubicin to the standard three-drug backbone plus CNS therapy.
 - (a) Children younger than 10 years receive dexamethasone as the corticosteroid of choice, as with standard-risk patients.
 - (b) Children 10 years and older receive prednisone as the steroid of choice because of the increased risk of osteonecrosis with dexamethasone in adolescent patients.
 - iii. After induction, patients may further be stratified according to age, response to therapy, or other characteristics (i.e., *BCR/ABL*) to receive more- or less-intense therapy.
 - b. Postinduction therapy
 - i. Postinduction therapy lasts several months and incorporates intermittent phases of intensity in an alternating fashion, such as the following:
 - (a) Consolidation, generally with cyclophosphamide, low- or intermediate-dose cytarabine, and mercaptopurine

- (b) Interim maintenance, with methotrexate given in one or more approaches depending on the patient's disease risk factors:
 - (1) Capizzi (escalating doses every 10 days)
 - (2) Intermediate dose (1000 mg/m²/dose intravenously over 24 hours)
 - (3) High dose (5000 mg/m²/dose intravenously over 24 hours)
 - (c) Reinduction or delayed intensification: Discontinuous dexamethasone should be used in lieu of continuous dexamethasone during delayed intensification for adolescents and young adults because of the increased risk of osteonecrosis.
 - (d) Maintenance
 - (1) Maintenance therapy, which typically continues for 2–2.5 years, is characterized by pulses of therapy wherein the absolute neutrophil count is targeted to a specific range using thiopurines together with other therapies.
 - (2) Adherence to oral chemotherapy (i.e., mercaptopurine) is critically important in maintenance. Poor adherence significantly increases relapse risk. Risk factors for nonadherence include children of Hispanic ethnicity, children younger than 12 years of age, and children in single-mother households.
 - (3) Recent data analyses suggest it is better to allow patients to simplify administration of oral mercaptopurine around their preferred schedule to increase adherence rates. Therefore, former recommendations of avoiding food and dairy and administering at night are no longer stringently recommended.
- ii. Pharmacogenomics in ALL
- (a) Preemptive pharmacogenomic testing should be part of the treatment of children with ALL.
 - (b) Guidelines and implementation tools are available from the Clinical Pharmacogenetics Implementation Consortium (CPIC; www.cpicpgx.org), including recommendations based on thiopurine methyltransferase (*TPMT*) and Nudix (nucleoside diphosphate linked moiety X)-type motif 15 (*NUDT15*) genotypes for patients receiving antimetabolites as part of the treatment of ALL.
 - (c) *TPMT* and *NUDT15*
 - (1) *TPMT* and *NUDT15* are enzymes involved in the biotransformation of antimetabolites used in the treatment of ALL, including mercaptopurine and thioguanine.
 - (2) Genotyping is recommended (over enzyme activity testing) to accurately predict the patient's phenotype from genotype.
 - (3) Patients with one or more no-function alleles are expected to have deficient or impaired enzyme activity, resulting in enhanced myelosuppression when given thiopurines. Intermediate metabolizers typically have one normal-function allele (**1*) and one no-function allele. Poor metabolizers will have two no-function alleles.
 - *TPMT* no-function alleles: **2*, **3A*, **3B*, **3C*, **4*
 - *NUDT15* no-function alleles: **2*, **3*, **4*
 - (4) Empiric dose reductions on the basis of genotype (and predicted phenotype) are warranted to prevent excess toxicity in children with cancer. For example, in patients prescribed mercaptopurine 75 mg/m²/day:
 - Poor metabolizers: Initiate mercaptopurine at a 10-fold dose reduction at a reduced frequency of thrice weekly (instead of once daily).
 - Intermediate metabolizers: Reduce starting dose by 30%–80%.
 - Reevaluate and adjust dose after 4–6 weeks on the basis of absolute neutrophil count and thioguanine metabolites.
 - See the CPIC guideline for additional details.

2. CNS prophylaxis
 - a. All children receive CNS prophylaxis with intrathecal chemotherapy because the CNS serves as a sanctuary site for disease and contributes to a high risk of CNS relapse.
 - b. Historical treatment approaches combined craniospinal radiation with intrathecal chemotherapy, resulting in a high rate of neurocognitive deficits.
 - c. Craniospinal radiation is now rarely used for frontline therapy. Newer treatment approaches minimize intrathecal chemotherapy exposure, when possible.
3. Special populations/other considerations
 - a. Bone marrow transplantation is reserved for children with specific high-risk features or after relapsed or progressive disease.
 - b. *BCR/ABL1* fusion is an uncommon disease in pediatric oncology.
 - i. Adding imatinib or dasatinib after induction better improves 3-year event-free survival (EFS) than in historical controls. Because of the significant transaminitis associated with imatinib in clinical trials, it must be given in a 2-week-on/2-week-off schedule in maintenance.
 - ii. *BCR/ABL1*-like (“Ph⁺-like”) disease is 3- to 4-fold more common than Ph⁺ disease in children and is characterized by other genetic aberrations such as *CRLF2* overexpression and *JAK1* or *JAK2* mutations (NOT the *BCR/ABL1* fusion).
 - c. Infants with ALL have extremely poor outcomes (22%–42% 6-year EFS). This is primarily believed to be because of the high frequency of mixed lineage leukemia rearrangements (around 80% of infants), the resistance of mixed lineage leukemia to treatment, the high rate of early relapsed or recurrent disease, and treatment-related mortality.
 - d. Children with T-cell disease have historically had poor outcomes (70%–80% EFS). Recent trials indicate that patients randomly assigned to receive nelarabine, Capizzi (escalating) doses of methotrexate, two extra doses of pegaspargase, and earlier cranial irradiation therapy had better outcomes than patients receiving high-dose methotrexate (5-year disease-free survival 91.5% vs. 85.3%, $p=0.005$).
 - e. Children with Down syndrome and ALL have an increased sensitivity to some chemotherapeutics such as methotrexate and anthracyclines.
 - i. Oral leucovorin is often given after intrathecal methotrexate during induction and consolidation.
 - ii. Courses of high-dose methotrexate are substituted with a lower, Capizzi-style methotrexate or intermediate doses of methotrexate.
 - iii. Anthracycline doses may be reduced or deferred in some protocols.
 - f. Adolescents and young adults have historically had poorer outcomes than younger children.
 - i. Several clinical trials have shown that adolescents and young adults have better survival when treated with pediatric-based protocols than with adult-based protocols.
 - ii. This increase in response is believed to be the result of a greater intensity in therapy.
 - g. Asparaginase/pegaspargase
 - i. Hypersensitivity reactions to pegaspargase may be more common in the postinduction treatment phase, particularly after a longer break between doses of pegaspargase, in high-risk patients. Rechallenging through careful desensitization may be an option for some children.
 - ii. Monitoring of asparaginase activity may help detect silent inactivation and anti-asparaginase antibodies and provide important information regarding which patients require a change from pegaspargase to asparaginase. Many centers premedicate (e.g., with antihistamines and corticosteroids) before second and subsequent doses to prevent hypersensitivity reactions.
4. Outcomes
 - a. Recent data for all children enrolled in COG clinical trials show that the 5-year OS has improved to 92.3%. This is a substantial improvement from the OS of 10% in the 1960s and the OS of around 83.7% in the early 1990s.

- b. Children and adolescents with relapsed disease have a poor prognosis.
 - i. Site of relapse is important in determining the prognosis, with marrow relapse more difficult to treat than extramedullary relapse.
 - ii. Time from diagnosis to relapse is also important in determining prognosis; relapse within 18 months is significantly worse than relapse more than 36 months from diagnosis.
 - iii. Immunophenotype is also an important prognostic factor. Relapsed T-cell disease is extremely hard to salvage.
 - iv. Blinatumomab was recently approved for relapsed/refractory and minimal residual disease–positive B-ALL. Recent data have suggested that blinatumomab is less toxic than and as effective as conventional chemotherapy for children and adolescents with relapsed/refractory B-ALL. Chimeric antigen receptor T-cell therapy is also approved for children and adolescents with relapsed/refractory disease. These and other novel immunotherapies have unique (at times aggressive) toxicity profiles (not discussed in this chapter).

Patient Case

Questions 4 and 5 pertain to the following case.

S.R. is a 3-year-old boy with trisomy 21 who presents to the ED with fatigue, pallor, petechiae, and pancytopenia. The team does a CBC with differential, a bone marrow aspirate and biopsy, and a lumbar puncture. His WBC is 12×10^3 cells/mm³. He is given a diagnosis of standard-risk ALL.

- 4. Which is best for administering methotrexate in S.R.?
 - A. He should not receive methotrexate because of the increased risk of severe mucositis in children with trisomy 21.
 - B. He should receive high-dose methotrexate and leucovorin rescue during consolidation because children with trisomy 21 have increased sensitivity to methotrexate.
 - C. He should receive intrathecal methotrexate with two doses of leucovorin rescue after each dose throughout therapy and six courses of high-dose methotrexate with leucovorin rescue during consolidation or interim maintenance.
 - D. He should receive intrathecal methotrexate throughout therapy plus two doses of leucovorin rescue after each dose during all phases except maintenance.
- 5. Which group of agents would S.R. best receive during induction?
 - A. Vincristine, dexamethasone, and pegaspargase.
 - B. Vincristine, prednisone, and pegaspargase.
 - C. Vincristine, dexamethasone, pegaspargase, and daunorubicin.
 - D. Vincristine, prednisone, pegaspargase, and daunorubicin.

V. ACUTE MYELOID LEUKEMIA

- A. Epidemiology
 - 1. About 730 children and adolescents (500 children, 230 adolescents) in the United States are given a diagnosis of AML each year.
 - 2. In children, AML is more common in Hispanic children and in the first 2 years of life.

B. Pathophysiology and Risk Factors

1. Similar to ALL, the cause of AML is generally unknown. The disease results in proliferation of abnormal myeloid, erythroid, monocytic, and megakaryocytic cell precursors, which may be the result of various genetic aberrations.
2. AML presents similarly to ALL with symptoms such as fever, malaise, bone pain, and cytopenias. In some patients, particularly those with acute promyelocytic leukemia, coagulopathies may be significant at diagnosis and until disease control is achieved. Chloromas may also be present at diagnosis.
3. Although the known risk factors are limited, they include exposure to benzene, exposure to radiation, and prior treatment with alkylating agents (e.g., cyclophosphamide/ifosfamide) or topoisomerase II inhibitors (e.g., etoposide).
4. Heritable risk factors associated with AML include Down syndrome, neurofibromatosis type 1, Fanconi anemia, Li-Fraumeni syndrome, and Diamond-Blackfan anemia.
5. Poor outcomes have been associated with pediatric patients older than 10 years at diagnosis, African American race, failure to achieve remission after induction, and abnormal body habitus (underweight or overweight according to BMI). Additional prognostic features of AML include the following:
 - a. Low risk: Core binding factor leukemias t(8;21), and inv(16) and NPM1-mutated AML
 - b. High risk: Monosomy 5; monosomy 7; 5qdel; *FLT3/ITD*, *KMT2A*, and *NUP98* rearrangements

C. Diagnosis

1. Similar to ALL, the diagnosis of AML is based on a pathologic evaluation of the blood and bone marrow before treatment.
2. Several subtypes of AML exist, though most subtypes are treated similarly. Two clinically relevant subtypes receive a different treatment approach: acute promyelocytic leukemia and Down syndrome–associated AML.
3. Staging is performed at diagnosis and throughout therapy, depending on response to various treatment approaches.
4. Cytogenetic and minimal residual disease evaluations are critical in ascertaining risk status and response to therapy.

D. Treatment and Outcomes

1. Treatment of AML is typically shorter and more intense than treatment of ALL. Phases of therapy include induction and intensification (or postremission).
 - a. Each phase of therapy includes cytarabine together with one or more additional conventional chemotherapeutic agents (e.g., daunorubicin, gemtuzumab/ozogamicin, mitoxantrone, etoposide).
 - b. Antimicrobial prophylaxis to support patients between cycles of therapy is critically important (see the Supportive Care section).
 - c. Allogeneic HSCT is indicated for patients with high-risk features after two or three courses of chemotherapy in first remission.
 - d. Maintenance therapy has not shown benefit for most patients with AML.
2. CNS prophylaxis is shorter and more limited than for ALL because of the lower incidence of CNS disease and because CNS involvement at diagnosis is not considered an independent prognostic factor. Core binding factor AML has a higher incidence of CNS disease and still the highest OS.
3. Clinical trials are actively exploring approaches to minimize treatment-related mortality and the usefulness of newer targeted agents, such as those targeting *FLT3/ITD*, in improving outcomes in children with AML.

4. Outcomes
 - a. Survival estimates for all patients are 50% for EFS and 60%–70% for OS. Survival after relapse or from refractory disease is low.
 - b. Treatment-related mortality is often related to infection, occurs in as many as 10% of all cases, and is higher in the adolescent and young adult population than in younger patients.
 - c. Children with obesity and those with a higher BMI have worse outcomes, largely because of an increased risk of infectious complications.
 - d. Common late effects include anthracycline-induced cardiotoxicity and secondary malignancies. Prevention of cardiotoxicity in patients with AML is of current clinical interest, with many centers routinely incorporating dexrazoxane prophylaxis as part of therapy.

VI. NON-HODGKIN LYMPHOMAS

- A. Epidemiology
 1. NHLs, or all lymphomas in children other than HL, are the third most common cancer in children and adolescents, representing about 5%–7% of all cancers in U.S. children. About 800 children and adolescents younger than 19 years are given a diagnosis of NHL each year.
 2. The median age at diagnosis is 10 years, affecting more males than females and more whites than African Americans.
 3. In contrast to adult NHL, most NHL cases in children are high-grade lymphomas. The predominant subtypes of NHL in children and adolescents are as follows:
 - a. Aggressive mature B-cell lymphoma
 - i. Burkitt lymphoma (40%)
 - ii. Diffuse large B-cell lymphoma (10%–20%)
 - b. Lymphoblastic lymphoma (20%)
 - c. ALCL (10%)
- B. Pathophysiology and Risk Factors
 1. The pathophysiology of NHL as a group is heterogeneous and directly related to the specific subtype of NHL. In general, cytogenetic abnormalities or infectious and immune-related changes are often thought to be a stimulus or cause of the disease.
 2. ALCL is characterized by both the presence of CD30 (all patients) and a translocation of the nucleolar phosphoprotein gene (*NPM*) with the *ALK* gene (more than 90% of patients). The *NPM-ALK* protein is thought to trigger antiapoptotic signals that work with other events to result in lymphoma. The presence of CD30 and the *NPM-ALK* protein is of clinical interest because of the availability of the newly approved targeted agents brentuximab vedotin and crizotinib.
 3. General predisposing risk factors for NHL include various congenital or acquired immunodeficiencies such as HIV infection and posttransplant immunosuppression.
- C. Diagnosis
 1. The approach to diagnosis varies by the type of lymphoma, but pathologic and cytogenetic analyses of the tumor are important in understanding the biology of the disease.
 2. The percentage of blasts on a bone marrow biopsy can provide a differentiation between lymphoblastic lymphoma and ALL.
 3. Staging also varies by the specific type of lymphoma. Most are staged using the Murphy staging system, which recognizes the extent of disease spread. Children with NHL are more likely than adults to have higher-grade tumors, extranodal involvement, and disseminated disease.

D. Treatment and Outcomes

1. Patients with advanced or bulky disease, such as a large mediastinal mass, are at risk of tumor lysis syndrome, airway compression, and superior vena cava syndrome. Supportive care should be provided to minimize the risk of, and treat, tumor lysis syndrome.
2. Multiagent conventional chemotherapy is the mainstay of treatment in children with NHL.
 - a. In general, children with lymphoblastic lymphoma respond better to treatments of longer duration, similar to the treatment of ALL. As such, contemporary protocols for ALL often include strata of children with lymphoblastic lymphoma.
 - b. Children with other types of NHL, such as Burkitt lymphoma, fare better with shorter, more intense therapy.
 - c. Therapy for ALCL is generally shorter and more intense; the role of maintenance therapy is unclear.
3. Targeted therapy with monoclonal antibodies and tyrosine kinase inhibitors has been investigated in several subtypes of NHL.
 - a. Crizotinib is FDA approved for pediatric patients older than 1 year with anaplastic lymphoma kinase (ALK)-positive, relapsed or refractory ALCL.
 - b. Rituximab added to standard chemotherapy improves survival in children and adolescents with high-grade, high-risk, mature B-cell NHL (e.g., Burkitt lymphoma).
4. Outcomes vary according to NHL subtype, though most subtypes have a good prognosis.
 - a. Diffuse large B-cell lymphoma: 90% OS. Poor prognostic features include high serum LDH at diagnosis, *c-myc* rearrangements, and a diagnosis of primary mediastinal B-cell lymphoma.
 - b. Lymphoblastic lymphoma: OS greater than 90% for low-stage disease and greater than 80% for advanced-stage disease. A poor prognosis is associated with CNS disease; therefore, all patients should receive CNS-directed chemotherapy.
 - c. Burkitt lymphoma: Greater than 85% OS; lower if CNS disease is present (about 80% OS). Poor prognostic features include high serum LDH at diagnosis, poor response to initial therapy, and specific cytogenetic abnormalities (i.e., partial duplication of 1q, 7q, and 13q-).
 - d. ALCL: 70%–85% OS from conventional chemotherapy; targeted agents (i.e., brentuximab vedotin and crizotinib) offer the potential to significantly improve outcomes, though this has not yet been proven in clinical trials.

VII. HODGKIN LYMPHOMA

- A. Epidemiology: HL is more common in adolescents than in children, with an estimated 800 new cases in adolescents and 400 new cases in children each year.
- B. Pathophysiology and Risk Factors
 1. Similar to NHL, the pathophysiology of HL is believed to be related to infectious, immune-related, and cytogenetic alterations. Unlike many other pediatric malignancies, a clear cytogenetic abnormality is not known.
 2. Infectious causes such as HIV, mononucleosis, or Epstein-Barr virus are often present in patients with newly diagnosed HL.
- C. Diagnosis
 1. Patients with HL often present with painless supraclavicular or cervical lymphadenopathy. Some patients may also present with generalized pruritus, fatigue, anorexia, weight loss, fever, and night sweats.

2. Diagnosis is based on pathologic analysis of the tumor and staging by imaging. Clinical criteria used in risk stratification include staging by Ann Arbor classification, the presence or absence of bulky disease, and the presence or absence of B symptoms (i.e., fever, weight loss, night sweats).
 3. Risk stratification of classic HL can vary by research consortium. General risk categories are as follows:
 - a. Low risk: Stages IA and IIA without bulky disease
 - b. Intermediate risk: Stages IB, IIB, and IIIA with or without bulky disease
 - c. High risk: Stages IIIB and IVB with or without bulky disease
- D. Treatment and Outcomes
1. Treatment includes multimodal, conventional chemotherapy and radiation, which is risk adapted to the patient to minimize toxicity while maintaining cure.
 2. Although HL is highly sensitive to radiation, conventional treatment approaches try to minimize radiation exposure because of the risk of late complications associated with radiation therapy (e.g., pulmonary disease, cardiac disease, secondary malignancies).
 3. Treatment is based on risk groups (i.e., low, intermediate, and high risk). Most protocols use two to four courses of chemotherapy with (or, in some cases, without) radiation. Some regimens are longer (e.g., eight cycles for high-risk disease). Individual protocols are not discussed in this chapter; readers are encouraged to review additional resources for details.
 4. Survival from HL is high, with as many as 97% of children and adolescents with newly diagnosed HL expected to be cured of the disease.
 5. Late effects from chemotherapy and radiation are of significant concern for survivors of HL. Children and adolescents should be followed throughout life for effects such as pulmonary fibrosis, cardiac disease (including heart failure), thyroid dysfunction, secondary malignancies (particularly breast cancer in female survivors who underwent mediastinal radiotherapy), and infertility.

VIII. CENTRAL NERVOUS SYSTEM TUMORS

- A. Epidemiology
1. CNS or brain tumors, as a group, are the second most common cancer in children and the third most common cancer in adolescents.
 2. More than 4000 children and adolescents are given a diagnosis of a primary brain or spinal cord tumor each year.
 3. Brain tumors are often categorized by the type of cells or tissues affected as well as the aggressiveness of the tumor.
 - a. Medulloblastoma is the most common malignant brain tumor in children, with around 400–450 new cases per year in the United States. The median age at diagnosis is 5–6 years. Males are affected almost twice as often as females.
 - b. High-grade and brain stem gliomas represent about 20%–25% of all brain tumors in children and are the second most common CNS tumor.
 - c. Ependymomas are the third most common brain tumor in children; recent data analyses suggest that ependymomas are nine molecularly different disease states.
 4. CNS tumors may be malignant or benign; however, even benign brain tumors can result in significant symptomatology for children and adolescents.
- B. Pathophysiology and Risk Factors
1. Like most other childhood cancers, the cause of CNS tumors is uncertain.
 2. There is a known association with radiation therapy and various genetic syndromes (e.g., Li-Fraumeni syndrome, neurofibromatosis type 1 or 2).

C. Diagnosis

1. Diagnosis is initiated on the basis of specific symptomatology, such as ataxia, seizures, headache, hydrocephalus, diplopia, changes in vision, behavioral changes, or significant nausea and vomiting.
2. Diagnostic techniques can include imaging only (e.g., MRI) for tumors located in certain parts of the brain. In some cases, a biopsy or tumor pathology from resection is warranted, when feasible.
 - a. Medulloblastoma is an embryonal tumor that typically arises in the midline cerebral vermis and has the potential to extend into the cerebellum, fourth ventricle, and brain stem. Leptomeningeal metastases occur in 25%–45% of patients.
 - i. Average-risk features include the following:
 - (a) Older age (i.e., older than 3 years)
 - (b) Localized disease at presentation with complete or near-complete resection
 - (c) Nodular or desmoplastic disease, or medulloblastoma with extensive nodularity
 - ii. High-risk features include the following:
 - (a) Patients who have metastatic disease or significant residual disease after surgery
 - (b) Large cell or anaplastic histology
 - (c) Genetic features such as *c-myc* amplification or 17p deletion
 - b. Gliomas can present as high-grade or brain stem gliomas.
 - i. Brain stem gliomas arise in the midbrain, pons, and medulla.
 - ii. Diffuse midline gliomas are diffuse astrocytomas that arise in the pons, thalamus, or spinal cord.
 - c. Ependymomas arise from ependymal cells that produce CSF, most commonly in or around the fourth ventricle.

IX. NEUROBLASTOMA**A. Epidemiology**

1. Neuroblastoma is the most common extracranial solid tumor of childhood, representing 7% of all childhood cancer cases each year.
2. The peak incidence of neuroblastoma is in children younger than 4 years, with the median age at diagnosis being 19 months.

B. Pathophysiology and Risk Factors

1. Neuroblastoma typically originates in the adrenal medulla or paraspinal sites (i.e., from the sympathetic nervous system).
2. Germline mutations in the *ALK* gene can occur in up to 12% of new cases. Around 6%–10% are sporadic *ALK* mutations, whereas 3%–4% are *ALK* amplifications.

C. Diagnosis**1. Presentation**

- a. Children with neuroblastoma often present with an abdominal mass or distension, pain, fever, weight loss, and hypertension. In some patients, pancytopenia, periorbital ecchymoses, Horner syndrome, heterochromia, proptosis, and nontender, bluish, subcutaneous nodules may also be present.
 - b. In some cases, a paraneoplastic syndrome like opsoclonus myoclonus ataxia syndrome may be present. Spinal cord compression, though rare, can occur and may require emergency intervention with corticosteroids, surgery, or radiation.
2. The diagnostic and staging approach involves biopsy of the tumor and the bone marrow, urine catecholamine analysis (HVA [homovanillic acid], VMA [vanillylmandelic acid]), and various imaging modalities (MRI, CT, bone scan, and MIBG [I(131)-metaiodobenzylguanidine scan]).

3. Risk stratification and staging
 - a. Treatment and expected survival vary significantly by risk groups.
 - b. Prognostic features important in risk stratification (and thus also in treatment) include the following:
 - i. Surgical staging (i.e., stages 1, 2, 3, 4, 4S)
 - ii. Age: Important breakpoints at 12 and 18 months of life, with older age conveying a poorer risk
 - iii. *MYCN* gene amplification
 - iv. DNA index
 - v. Shimada histopathology
 - vi. Race or ethnicity (African American race is a poor-risk feature)
- D. Treatment and Outcomes
 1. Low-risk patients are typically treated with surgery and long-term observation.
 2. Intermediate-risk patients require surgery, together with four to eight cycles of conventional multiagent chemotherapy.
 3. High-risk patients require several phases of therapy and yet still have only a 50% chance of long-term survival. Phases of therapy include the following:
 - a. Induction: Five or six cycles of conventional, multiagent chemotherapy
 - b. Consolidation: Surgery, radiation, and high-dose chemotherapy, followed by tandem autologous stem cell transplantation
 - c. Maintenance: Six cycles of immune therapy, including combinations of dinutuximab, aldesleukin, and isotretinoin

Patient Case

6. A 6-year-old girl with a diagnosis of *ALK*-positive high-risk neuroblastoma is referred to your institution from another pediatric hospital. She received one cycle of chemotherapy before transfer to your institution. Which is the optimal approach to managing her disease?
 - A. She should receive an additional five cycles of multiagent, conventional chemotherapy; surgery; and radiation.
 - B. She should receive an additional five cycles of multiagent, conventional chemotherapy; surgery; radiation; high-dose chemotherapy with autologous stem cell rescue; and maintenance isotretinoin.
 - C. She should receive an additional five cycles of multiagent, conventional chemotherapy; surgery; radiation; high-dose chemotherapy with autologous stem cell rescue; and maintenance immunotherapy with aldesleukin, dinutuximab, and isotretinoin.
 - D. Standard treatment for children with high-risk neuroblastoma is typically limited to palliative chemotherapy and radiation.

X. WILMS TUMOR

- A. Epidemiology
 1. Wilms tumor, or nephroblastoma, is the most common renal tumor and is expected to affect about 500 children in the United States each year.
 2. The peak incidence of Wilms tumor is at 2–3 years of age, with almost all cases in children younger than 6 years.
 3. Most Wilms tumor cases are unilateral, with only 5%–10% presenting as bilateral disease. Most cases of bilateral disease are familial in origin.

B. Pathophysiology and Risk Factors

1. Wilms tumor is thought to be related to a functional loss of tumor suppressor genes. Around 1%–2% of all cases are believed to be of familial origin.
2. Risk factors for Wilms tumor include a family history of disease, WAGR (Wilms, aniridia, genitourinary malformations, and retardation), Denys-Drash (*WT1* mutations), hemihypertrophy, and Beckwith-Wiedemann syndrome.

C. Diagnosis

1. Children with Wilms tumor often present with a painless abdominal mass, with or without hematuria.
2. Diagnostic techniques include imaging and surgical removal with pathologic analysis. Surgical staging and tumor pathology are important in determining the patient's risk category, prognosis, and treatment approach. However, tumor pathology – namely, the presence or absence of anaplasia – is the single most important prognostic factor in children with Wilms tumor.
3. Poor prognostic features include metastatic or bilateral disease, anaplastic histology, nodal involvement, and LOH for 1p or 16q.

D. Treatment and Outcomes

1. Treatment varies depending on tumor size, location, spread, and histology. Effective treatments include surgery, radiation, and conventional chemotherapy.
2. Patients with unilateral disease undergo partial or complete nephrectomy, when feasible. Patients with bilateral or multicentric unilateral disease should receive up to 12 weeks of chemotherapy before renal-sparing surgery.
3. Local radiation to the tumor bed (and, in some cases, sites of metastases) should be given for stage III and higher.
4. Table 1 shows the approach to chemotherapy, which is based on stage, histology, age, tumor weight, and LOH at 1p and 16q.

Table 1. Approach to Chemotherapy for Wilms Tumor

Regimen	Agents	Eligible Patient Groups
EE4A	Vincristine Dactinomycin (19 wk)	• Stage I, favorable histology, age < 2 yr, tumor weight ≥ 550 g, no LOH at 1p and 16q • Stage I, favorable histology, age ≥ 2 yr, any tumor weight, no LOH at 1p and 16q
DD4A	Vincristine Dactinomycin Doxorubicin (25 wk)	• Stage I, favorable histology, any age or tumor weight, LOH at 1p and 16q • Stage I, focal anaplasia or diffuse anaplasia • Stage II, favorable histology, any age or tumor weight, LOH at 1p and 16q • Stage II or stage III, focal anaplasia • Stage III, favorable histology, any age or tumor weight, no LOH • Stage IV, favorable histology, any age or tumor weight, no LOH at 1p and 16q plus a rapid response to lung radiation
M	Vincristine Dactinomycin Doxorubicin Cyclophosphamide Etoposide (31 wk)	• Stage III, favorable histology, any age or tumor weight, LOH at 1p and 16q • Stage IV, favorable histology, any age or tumor weight, no/any LOH at 1p and 16q, no rapid response to lung radiation

Table 1. Approach to Chemotherapy for Wilms Tumor (*continued*)

Regimen	Agents	Eligible Patient Groups
UH-1	Vincristine Dactinomycin Doxorubicin Cyclophosphamide Carboplatin Etoposide (30 wk)	• Stage II or stage III, diffuse anaplasia
UH-2	Vincristine Dactinomycin Doxorubicin Cyclophosphamide Carboplatin Etoposide Vincristine Irinotecan (30 wk)	• Stage IV, diffuse anaplasia

LOH = loss of heterozygosity.

- Survival for most patients with Wilms tumor is excellent, with OS greater than 90% for the group as a whole.
- Late treatment effects are a significant problem for survivors of Wilms tumor, including cardiac failure, impaired renal function, infertility, increased risk of secondary malignancies, and pregnancy-related complications such as pregnancy-related hypertension, premature delivery, and low-birth-weight infants.

Patient Case

Questions 7 and 8 pertain to the following case.

J.W. is a 2-year-old girl who was referred to the clinic from her primary pediatrician. One week ago, her grandmother noticed a nontender mass in her abdomen while bathing her. K: J.W. is afebrile and otherwise well appearing. Ultrasonography revealed a large mass arising from the right kidney that appeared to be a Wilms tumor. There was no involvement of the inferior vena cava, and there were no visible metastases. Biopsy of the tumor after surgical excision confirmed a stage II, favorable-histology Wilms tumor (weighing 600 g), with LOH at 1p and 16q.

- Which is most appropriate for treating J.W., using the abbreviations in Table 1?
 - EE4A for 19 weeks.
 - DD4A for 25 weeks.
 - Regimen M for 31 weeks.
 - UH-1 plus the VI window (UH-2) for 30 weeks.
- Which is most accurate regarding the late outcomes that J.W. might experience after the treatment selected in the previous question?
 - Late cardiotoxicity (heart failure) from doxorubicin.
 - Chronic diarrhea from irinotecan.
 - Hearing loss from carboplatin.
 - Secondary AML from etoposide.

XI. OSTEOSARCOMA

A. Epidemiology

1. Osteosarcoma is the most common bone tumor in children and adolescents, affecting around 400 patients each year.
2. The peak incidence of disease is bimodal with the first peak in the second decade of life and a second peak after 60 years of age.

B. Pathophysiology and Risk Factors

1. Osteosarcoma arises from the mesenchymal stem cell that normally differentiates into bone, cartilage, or fibrous tissue.
2. Several risk factors have been identified, including the *RBI* mutation, Li-Fraumeni syndrome (*p53* mutation), Paget disease, Diamond-Blackfan anemia, and prior treatment with ionizing radiation.

C. Diagnosis

1. Osteosarcoma often presents as pain, swelling, a mass, or redness around a joint or bone. As many as 10%–15% of new patients may present with a pathologic fracture at diagnosis.
2. Osteosarcoma typically affects the growing ends of the long bones or the metaphysis, specifically the distal femur, proximal tibia, and proximal humerus.
3. About one in five children will be given a diagnosis of metastatic disease at presentation, with the most common site being lung metastases.

D. Treatment and Outcomes

1. Although there are several histologic classifications, treatment is based solely on the patient's designation as having localized or metastatic disease at diagnosis.
2. Osteosarcoma is relatively resistant to radiation; effective treatment modalities include surgery and selected chemotherapeutic agents.
3. Most patients receive neoadjuvant chemotherapy, local control with surgery, and subsequent adjuvant chemotherapy according to the extent of tumor necrosis at the time of surgery. Adjuvant chemotherapy should be dosed using the pre-amputation weight.
 - a. The most recent COG approach for localized disease included cisplatin/doxorubicin alternated with high-dose methotrexate in the pre- and postoperative settings.
 - b. There is no well-defined approach to managing metastatic disease; many centers treat patients with metastatic disease similarly to those with localized disease.
 - c. Preoperative (neoadjuvant) chemotherapy should be used in all patients. Summary points include the following:
 - i. Triple-agent regimens are superior to doublet regimens.
 - ii. Triple regimens without high-dose methotrexate are inferior to those with high-dose methotrexate.
 - iii. Four-agent regimens are not superior to triple-agent regimens.
 - d. Postoperative (adjuvant) chemotherapy effectively prevents relapse after resection of localized tumors. According to recent trial data, there is no survival benefit for interferon or the addition of ifosfamide and etoposide.
4. Prognosis is considerably worse for patients having metastatic disease at diagnosis than for those having localized disease; long-term survival rates are 60%–70% for localized disease versus 20%–25% for metastatic disease.
5. Histologic response to therapy at the time of surgery is predictive of responsiveness to therapy and thus OS, with patients achieving greater than 90% necrosis demonstrating the best outcomes.
6. Late effects from chemotherapy may include secondary malignancies, infertility, nephrotoxicity, cardiotoxicity, hearing loss, and neurotoxicity.

Patient Case

Questions 9 and 10 pertain to the following case.

A.J. is a 16-year-old male adolescent who presents to the ED with swelling and tenderness around his right knee. He was unexpectedly thrown off his horse earlier in the day. He has been unable to put pressure on his right leg and currently rates his pain as 10/10. Radiography of the leg reveals a Codman triangle with a fracture in the distal femur. He is given a preliminary differential diagnosis of osteosarcoma and sent for a biopsy.

9. Which is the most likely treatment approach for a patient such as A.J. with newly diagnosed osteosarcoma?
 - A. Neoadjuvant chemotherapy, followed by surgery as local control; then adjuvant chemotherapy.
 - B. Neoadjuvant chemotherapy, followed by radiation as local control; then adjuvant chemotherapy.
 - C. Chemotherapy followed by radiation.
 - D. Palliative radiation therapy alone.
10. The treating physician opts to initiate therapy with a course of “AP” chemotherapy (doxorubicin 37.5 mg/m²/day and cisplatin 60 mg/m²/day for 2 days). The patient has no known medication allergies, takes no other medications at home, and has no contraindications to the receipt of corticosteroids. Which is the most appropriate antiemetic regimen for A.J.?
 - A. Aprepitant, dexamethasone, and ondansetron.
 - B. Ondansetron, dexamethasone, and promethazine.
 - C. Dexamethasone, palonosetron, and promethazine.
 - D. Dexamethasone, ondansetron, and nabilone.

XII. EWING TUMORS AND EWING SARCOMA

- A. Epidemiology
 1. The Ewing family of tumors, traditionally Ewing sarcoma, is the second most common bone cancer in children and adolescents and affects around 200 new patients each year.
 2. The peak incidence is at around 15 years of age.
- B. Pathophysiology and Risk Factors
 1. Ewing sarcoma is a peripheral primitive neuroectodermal tumor in the Ewing sarcoma family of tumors.
 2. The cause of the tumor is generally unknown, but it is characterized by the presence of the *EWS/FLI* oncoprotein.
- C. Diagnosis
 1. Similar to osteosarcoma, Ewing sarcoma often presents as pain, swelling, a mass, or redness around the affected tumor site. In contrast to osteosarcoma (which is most common in the long bones), Ewing sarcoma is more common in the axial skeleton and arises from the diaphysis of bones.
 2. Some patients may present with systemic symptoms such as fatigue, anorexia, fever, weight loss, or other complications associated with the primary site of the tumor.
 3. About one-fourth of patients have metastatic disease at diagnosis, with metastases commonly found in the bone, bone marrow, and lungs.
 4. Ewing sarcoma is characterized by an “onion-skin” periosteal reaction on radiography and the presence of the *EWS/FLI* oncoprotein, t(11;22)(q24;q12).

5. Poor prognostic features include metastatic disease, male sex, Ewing sarcoma as a secondary malignancy, primary tumor larger than 8 cm, or tumor in an unfavorable site (e.g., pelvic or centrally located tumor).

D. Treatment and Outcomes

1. Patients with Ewing sarcoma are treated according to the distinction of having either localized or metastatic disease at diagnosis.
2. Treatment typically includes induction (i.e., neoadjuvant) chemotherapy, local control with surgery and/or radiation, and subsequent consolidation (i.e., adjuvant) chemotherapy.
 - a. The standard chemotherapy approach consists of vincristine, doxorubicin, and cyclophosphamide alternating with cycles of etoposide and ifosfamide.
 - b. For patients with no known metastases, 5-year EFS is significantly improved when cycles are administered every 14 days instead of every 21 days, supported by growth factors (73% vs. 65%, respectively).
 - c. For patients with metastases, clinical trials have shown no benefit to adding ifosfamide and etoposide to a standard backbone of vincristine, cyclophosphamide, and either doxorubicin or dactinomycin, with EFS and OS of around 20% and 30%, respectively.
 - i. Despite this lack of benefit, many clinicians still opt to intensify chemotherapy for patients with metastatic disease, as is done for patients without metastases.
 - ii. Almost 80% of patients will have disease relapse within 2 years of therapy; survival after relapse is dismal, with 5-year EFS estimates of 7% for children whose disease relapses within 2 years of diagnosis.

XIII. RHABDOMYOSARCOMA

A. Epidemiology

1. Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents, with about 350 children and adolescents given this diagnosis each year.
2. The incidence of rhabdomyosarcoma peaks at 2–5 years of age.
3. The two common subtypes of rhabdomyosarcoma have significantly different prognostic outlooks. The most common subtype, embryonal rhabdomyosarcoma, occurs in about 75% of cases and typically carries a better prognosis than the alveolar subtype (about 16% of all cases).

B. Pathophysiology and Risk Factors

1. Rhabdomyosarcoma arises from mesenchymal tissue and imitates striated smooth muscle fibers.
2. Rhabdomyosarcoma may be sporadic or associated with genetic conditions such as familial mutations in *p53* (Li-Fraumeni syndrome), Costello syndrome (germline *HRAS* mutations), Beckwith-Wiedemann syndrome, and neurofibromatosis type 1. Genetic mutations have been associated with both embryonal tumors (LOH at 11p15) and alveolar tumors (t(2;13)(q35;q14) and t(1;13)).

C. Diagnosis

1. Patients may present with a mass, bump, or swelling in the location of the tumor. Patients may also present with symptoms involving the location of the tumor, such as proptosis for orbital tumors or hematuria for tumors arising from the genitourinary system.
2. Staging is based on tumor histopathology, imaging, surgical staging, and location of the primary tumor.
3. Risk groups include low-, intermediate-, and high-risk populations. Treatment is primarily based on risk stratification.

D. Treatment and Outcomes

1. A multimodal approach is critical to the treatment success for rhabdomyosarcoma.
 - a. Low risk
 - i. Vincristine, dactinomycin with or without radiation for 48 weeks, or
 - ii. Vincristine, dactinomycin, cyclophosphamide (VAC) for 13–46 weeks (children with stage 3, group I or II disease and children with stage 1, group III non-orbital disease may require a longer therapy duration)
 - b. Intermediate risk
 - i. VAC plus radiation
 - ii. Although several trials have tried to improve survival by incorporating alternative agents (e.g., topotecan, ifosfamide, etoposide), none has shown improved success.
 - c. High risk
 - i. VAC plus radiation or clinical trial
 - ii. No benefit has been shown from adding several agents to VAC therapy, including melphalan, topotecan, etoposide, doxorubicin, and irinotecan. There is no benefit to use of high-dose chemotherapy with stem cell rescue.
2. Treatment of an individual patient varies according to risk category, which considers tumor location, tumor spread or the presence of metastases, and histopathology.
3. The 5-year EFS for low-, intermediate-, and high-risk groups is about 95%, 65%, and 15%, respectively. Survival after relapse is very poor (17%).
4. Temsirolimus may offer promise (over bevacizumab) when added to vinorelbine and cyclophosphamide in patients with first relapse or disease progression with an unfavorable prognosis.

XIV. RETINOBLASTOMA**A. Epidemiology**

1. Retinoblastoma is the most common intraocular tumor of childhood, with about 300 children in the United States given a diagnosis each year.
2. The median age at diagnosis does vary, however, with sex: around 1 year of age for females and 2 years of age for males. The median age of diagnosis for all bilateral cases is 1 year of life.
3. Hereditary retinoblastoma is typically diagnosed within the first 2.5 months of life.

B. Pathophysiology and Risk Factors

1. Retinoblastoma is commonly associated with the *RBI* germline mutation. Patients with the *RBI* gene are at an increased risk of a second primary cancer (particularly osteosarcoma) or secondary malignancies resulting from radiation therapy. Almost 40% of all cases are associated with the autosomal-dominant *RBI* germline mutation; this is subdivided by unilateral (15% of all cases) and bilateral (25% of all cases, but almost 100% of the bilateral cases).
2. All patients with this mutation and their direct family members should receive genetic counseling about the risk of this and other tumors associated with the *RBI* gene.

C. Diagnosis

1. Patients with retinoblastoma commonly present with leukocoria, strabismus, ocular inflammation, proptosis, or anterior chamber changes.
2. Children with a family history of retinoblastoma should receive eye examinations on a rigorous schedule, which may include within days after birth, at 6 weeks of age, every 2–3 months until 2 years of age, and every 4 months until 3 years of age.

3. Diagnosis is based on a detailed examination under anesthesia with a dilated pupil and scleral indentation for optimal examination of the retina. Pathologic confirmation is not required. Imaging with ultrasonography and MRI can help determine the presence of extraocular extension; CT should be avoided because of the increased risk of secondary malignancies.
4. Current staging is based on the International Classification of Retinoblastoma (i.e., groups A–E), which describes the extent of tumor seeding within the retinal cavity and subretinal space.

D. Treatment and Outcomes

1. Treatment varies depending on the clinical group, with consideration given to tumor size, location, and extent of seeding or spread. Effective treatment modalities include surgery, radiation, and chemotherapy. Treatment can be systemic, localized, or a combination of both.
 - a. Surgery
 - i. Surgery for retinoblastoma includes enucleation of the eye.
 - ii. Contemporary treatment approaches aim to reduce the number of enucleations, when possible, because of the increased morbidity to the patient and caregiver. Ocular-sparing approaches, such as tumor-directed chemotherapy, are of significant interest.
 - b. Radiation
 - i. Radiation for retinoblastoma may include external beam radiation therapy with IMRT (intensity-modulated radiation therapy), stereotactic radiation, or proton beam radiotherapy.
 - ii. Other local control options include cryotherapy and local laser therapy.
 - c. Chemotherapy
 - i. The most commonly used agents for systemic chemotherapy are carboplatin, etoposide, and vincristine.
 - ii. Investigators aim to reduce the etoposide exposure because of the risk of secondary malignancies, though the risk of secondary AML is relatively low in this population.
 - iii. Local chemotherapy by intravitreal and intra-arterial (i.e., through the ophthalmic artery) routes has been investigated with agents such as melphalan, topotecan, and carboplatin, and it is of great interest because of the ability to reduce systemic chemotherapy exposure and potentially increase the ability to spare vision.
2. The primary treatment aim is to achieve cure but with the added goal of preserving vision and minimizing late effects from therapy. Late effects can include decreased orbital growth, visual field defects, chemotherapy-induced hearing loss, and secondary malignancies.
3. Contemporary treatment approaches try to provide more localized and less systemic therapy, when possible, through intra-arterial or intravitreal chemotherapy.
4. The expected 5-year EFS for localized disease is greater than 90%. Disseminated disease is uncommon; however, children with disseminated disease fare poorly, with 1-year EFS rates of 40% for orbital/regional disease, 20% for distant metastatic disease, and almost 0% for CNS metastases.
5. The most common cause of death in children with retinoblastoma is a second malignancy. The most common second malignancies are usually osteosarcoma, soft tissue sarcoma, and melanoma. The sarcomas are primarily related to radiation therapy in children, with as many as 30% of patients experiencing a second malignancy after treatment with radiation.

XV. HEMATOPOIETIC STEM CELL TRANSPLANTATION

A. Overview in Pediatric Oncology

1. Indications for and outcomes from HSCT vary between children and adults.
2. Children represent a small percentage of all patients undergoing transplantation.

B. Pediatric HSCT Indications for Children

1. Allogeneic HSCT
 - a. Marrow or peripheral blood stem cells from a matched sibling donor is the optimal stem cell source for an allogeneic HSCT. If a matched sibling is not available, marrow from a matched unrelated donor or a cord blood transplant may be considered. A haploidentical HSCT is generally not preferred, though it can be used if no other source is available.
 - b. The most common indications for allogeneic HSCT in children are hematologic malignancies such as ALL and AML.
 - c. Children with hematologic malignancies who may benefit the most from allogeneic HSCT include those with ALL or AML whose induction fails, those with ALL whose disease relapses within 36 months of diagnosis, or those with ALL or AML in first remission with high-risk features.
 - d. Children with nonmalignant disorders can also benefit from allogeneic HSCT. Disorders include sickle cell disease, metabolic storage disorders (e.g., mucopolysaccharidosis type I), Fanconi anemia, aplastic anemia, and severe combined immunodeficiency syndrome.
2. Autologous HSCT: Warranted in children with high-risk neuroblastoma as part of the routine treatment approach. Other pediatric malignancies that may warrant autologous HSCT include brain tumors (e.g., medulloblastoma) and relapsed tumors such as HL or germ cell tumors.
3. Most patients' disease should be in remission or patients should have only minimal disease present before continuing to transplantation. The tumor must be considered chemotherapy sensitive for consideration of HSCT.
4. Adoptive cell transfer immunotherapy
 - a. Recently, chimeric antigen receptor (CAR) T-cell therapies were approved for adults and children with relapsed hematologic malignancies.
 - b. CAR T-cell therapies are a genetically modified autologous T-cell immunotherapy intended to treat patients by targeting certain cell markers, or antigens, like CD19.
 - c. Patient T cells are collected, sent to a specific laboratory to be engineered, and returned to the clinical site. Patients receive a lymphodepleting regimen of chemotherapy, followed by infusion of the cells.
 - d. Management of significant adverse effects, such as cytokine release syndrome (CRS), is critical in the first several days after the infusion. Management of CRS typically includes supportive care and pharmacologic therapies to abrogate cytokine storm. Tocilizumab, an interleukin-6 receptor antagonist, is FDA approved for the management of CRS in patients receiving CAR T-cell therapies and should be kept on hand in centers providing CAR T-cell therapies. For more severe cases of CRS, corticosteroids can be considered (e.g., dexamethasone); however, they should be reserved for more severe reactions because steroids dramatically affect T-cell expansion and may reduce the clinical efficacy of CAR T-cell therapy.

C. Supportive Care Issues

1. Graft-vs.-host disease (GVHD) is perhaps one of the most challenging supportive care aspects after transplantation. GVHD can present as acute or chronic, depending on the timeline of presentation after transplantation.
 - a. The incidence of acute GVHD (historically defined as within the first 100 days after transplantation) varies widely, with rates of 20%–80% in children after allogeneic transplantation. All patients with an allogeneic HSCT from a non-T-cell depleted graft should receive prophylaxis for acute GVHD.
 - b. Chronic GVHD (historically defined as more than 100 days after transplantation) is less common in children than in adults, occurring in about one in every four children receiving a transplant. Risk factors for developing chronic GVHD include the use of peripheral blood stem cells, increasing donor-recipient HLA disparity, intensive conditioning, a female donor to male recipient transplant, and older donor age.

2. Other important supportive care issues in the posttransplant setting include the management of mucositis, pain, nutrition, emesis, SOS, hemorrhagic cystitis, infectious complications, psychosocial issues, and normal educational and developmental aspects of childhood. See the Supportive Care section for additional details on managing supportive care issues.
3. All children should receive long-term follow-ups after HSCT to monitor for the late effects of chemotherapy and radiation and the adverse effects of transplantation. Some of the more common late effects after HSCT include thyroid dysfunction, cataracts, gonadal dysfunction, sterility, pulmonary disorders, osteopenia, and secondary malignancies.

Patient Case

11. Which patient would be most appropriate for HSCT?
- A. 10-month-old boy with intermediate-risk neuroblastoma who has responded to conventional chemotherapy.
 - B. 7-year-old girl with AML with abnormal cytogenetic features in first remission.
 - C. 16-year-old female adolescent with sickle cell disease who has no matched sibling donors.
 - D. 5-year-old boy with average-risk ALL who has just achieved remission after induction therapy.

XVI. SICKLE CELL DISEASE

- A. Epidemiology
 1. It is estimated that 90,000–100,000 individuals in the United States have sickle cell disease.
 2. Routine newborn screening for sickle cell disease in each of the 50 states detects about 2000 new cases each year. Sickle cell disease occurs in about 1 in every 500 African American births and 1 in every 36,000 Hispanic births.
 3. Sickle cell trait occurs much more often, in an estimated 1 in 12 African American births.
 4. Progress has been substantial over the past several decades; survival has improved from about age 14 years in the 1970s to at least 4 times that today.
- B. Pathophysiology and Risk Factors
 1. Sickle cell disease is a heritable disorder characterized by the abnormal sickling of RBCs because of deoxygenation.
 2. Hemoglobin is typically composed of two α -globin chains and two β -globin chains. Sickle cell anemia results from a homozygous mutation in the β -globin chain. Sickle cell disease can result from a compound heterozygous mutation of HbS with another f3-globin mutation (e.g., sickle- β -thalassemia or HbSC).
 3. Patients with one hemoglobin A or normal hemoglobin and one HbS are characterized as having sickle cell trait. These patients are commonly asymptomatic or mildly symptomatic.
 4. Because the disease is heritable, risk factors include a direct family history of sickle cell disease. Sickled RBCs are resistant to infection with *Plasmodium falciparum*. As a result, the sickle cell gene has prevailed as a survival mechanism and is prevalent in areas of the world with a high incidence of malaria.
- C. Diagnosis
 1. In the United States, sickle cell disease is included as part of neonatal screening. Early diagnosis allows providers to provide caregiver education and early interventions to help prevent or minimize severe complications of the disease.

2. Children born outside the United States may be given the diagnosis upon newborn screening or at a delayed point after an initial sickling-related event, such as vaso-occlusive crisis, hemolytic anemia, or infectious-related complications such as meningitis, invasive pneumococcal disease, or dactylitis.

D. Treatment

1. Treatment includes both preventive maintenance and treatment of the complications of the disease.
 - a. Preventive maintenance includes regularly scheduled office visits with examinations and caregiver education, childhood immunizations, folic acid supplementation in the setting of chronic hemolysis, and penicillin prophylaxis (from 2 months of age through at least 5 years; indefinitely in patients with asplenia or those with a history of severe pneumococcal infection).
 - b. Hydroxyurea therapy should be offered to all patients 9 months and older. Hydroxyurea therapy requires a carefully titrated dose that is closely monitored for adverse events such as myelosuppression.
 - c. Prescription-grade L-glutamine oral powder is approved to reduce the complications of sickle cell disease in adults and pediatric patients 5 years and older.
 - i. Results from a randomized, double-blind, multicenter trial showed a mild but statistically significant reduction in the median number of sickle cell crises and number of hospitalizations.
 - ii. L-glutamine provided a statistically significant and meaningful reduction in the median number of hospital days and percentage of patients affected by acute chest syndrome.
 - d. Other novel agents that have improved clinical outcomes in adolescents and adults with sickle cell disease include the following:
 - i. Voxelotor: Indicated for the treatment of sickle cell disease in adults and pediatric patients 12 years and older
 - ii. Crizanlizumab: Indicated to help reduce the frequency of vaso-occlusive crises in adults and pediatric patients 16 years and older with sickle cell disease
 - e. RBC transfusions may be necessary for patients with acute episodes of anemia to provide symptomatic relief or minimize complications from hemolytic crisis.
 - i. Transfusions should be carefully dosed to the patient's baseline Hgb to minimize the risk of volume overload.
 - ii. Chronic transfusions are used in patients with a history of a stroke to prevent stroke recurrence.
 - iii. Iron chelation with oral or injectable iron chelators (i.e., deferasirox and deferoxamine, both of which are indicated for use in children; deferiprone is only indicated in adults) may be required in patients receiving multiple or chronic transfusions. A general indicator of the potential need for chelation is a cumulative volume of 120 mL/kg of packed RBCs.
 - f. Additional treatment includes management of vaso-occlusive crises (i.e., splenic or hepatic sequestration, pain crisis, and aplastic crisis), infectious complications, and acute chest syndrome.
 - i. Vaso-occlusive crises are treated symptomatically as clinically indicated and can include volume resuscitation, RBC transfusion, and pharmacologic or nonpharmacologic pain therapy.
 - ii. Fever and infectious complications should be addressed quickly with antibiotic therapy, cultures, and imaging. Broad-spectrum antibiotics with coverage for encapsulated organisms should be used because of the risk of splenic dysfunction. *Salmonella* and *Staphylococcus* coverage should be considered for patients with symptoms of dactylitis or osteomyelitis.
 - g. Many other complications from sickle cell disease exist but are not included in this chapter; readers are encouraged to review additional sources such as the 2014 NIH report on the evidence-based management of sickle cell disease (see References) for detailed information.
2. In rare cases, allogeneic stem cell transplants have been used for patients with severe disease. The biggest barrier to transplantation is the lack of HLA-matched sibling donors who are unaffected by the disease.

XVII. IRON DEFICIENCY ANEMIA**A. Epidemiology**

1. Iron deficiency in children is the most common nutrient concern in low- and middle-income countries. It is also common in higher-income countries, affecting up to 15% of children 1–2 years of age and 11% of female adolescents.
2. Iron deficiency without anemia and iron deficiency anemia can have harmful and potentially long-lasting effects on neurodevelopment.
3. Iron requirements for infants (0–12 months of life) and children 1–3 years of age vary substantially. Iron requirements as determined by the Institute of Medicine are as follows:
 - a. Preterm infants require an increasing amount of iron with decreasing gestational age; however, iron stores accumulated with any blood transfusions must be considered.
 - b. Term infants from birth to 6 months can be sustained on the amount of iron in human breast milk (about 0.27 mg/day). By 6 months of age and through 12 months of life, iron requirements increase to around 11 mg/day.
 - c. Children 1–3 years of age require about 7 mg/day of iron.

B. Presentation, Screening, Prevention, and Treatment**1. Presentation**

- a. In the United States, patients are often asymptomatic, and their disease is diagnosed with a screening blood test at a well-child visit.
- b. Rarely, infants may present symptomatically with irritability, lethargy, pallor, poor feeding, and tachypnea. Older children may present with exercise intolerance or pica (i.e., consumption of non-food items such as soil, sand, or clay).
- c. Female adolescents may develop iron deficiency as a result of chronic menstrual blood loss, particularly in the setting of abnormal uterine bleeding.

2. Screening and diagnosis

- a. The American Academy of Pediatrics recommends universal screening at 1 year of age with measurement of serum hemoglobin.
 - i. Infants and children 1–3 years of age with significant risk factors or Hgb less than 11 g/dL should receive additional follow-up.
 - ii. Infants or children 1–3 years of age consuming excess cow's milk (greater than 16 oz/day) or those with a diet low in iron (e.g., low-meat diet) may be at risk of iron deficiency anemia. Dietary changes (restriction of cow's milk, increased iron intake) should be considered to prevent or mitigate iron deficiency.
- b. Patients typically present with a microcytic anemia, clinical risk factors, and low serum ferritin (less than 15 ng/mL). Response to therapeutic dosing of oral iron supplementation may aid in the diagnosis of iron deficiency anemia.

3. Prevention and treatment

- a. Preterm infants who consume human milk should be given oral elemental iron (2 mg/kg/day as fortified foods or supplementation) starting at 1 month of life and lasting through 12 months. Infant formulas typically include a sufficient dose of iron supplementation, though a small percentage of these formula-fed infants may require iron supplementation as well.
- b. Exclusively breastfed term infants (or infants receiving more than one-half as breast milk with the balance as formula) should receive iron supplementation (1 mg/kg/day of elemental iron) starting at 4 months of life and continuing until the introduction of iron-containing foods.
- c. Infants, children 1–3 years of age, and children older than 4 years with a diagnosis of iron deficiency anemia should receive a starting dose of 3 mg/kg/day of oral elemental iron (preferably as ferrous sulfate) given once daily at least 2 hours before or after meals and without dairy products.

- d. Adolescents may be given 65–130 mg of elemental iron once daily (also preferably as ferrous sulfate).
- e. Patients who are intolerant of or who do not respond to oral therapy may require parenteral iron replacement. Several parenteral products are available with variable safety and efficacy.

XVIII. HEMOPHILIAS

A. Epidemiology

1. Hemophilia A and B are heritable X-linked recessive disorders that result in absent or decreased levels of factor VIII (hemophilia A) or factor IX (hemophilia B). Severe hemophilia is almost exclusively a disease of males, though females are occasionally affected. In addition, up to one-fourth of female carriers who are heterozygotes may have symptoms of mild hemophilia.
2. Hemophilia can result in excessive bleeding if not appropriately prevented or treated with replacement therapy.
3. Of all hemophilia cases, around 80%–85% are hemophilia A, or classic hemophilia. The remaining cases (15%–20%) are hemophilia B, also known as Christmas disease.

B. Pathophysiology and Risk Factors

1. Factors VIII and IX are important in the formation of thrombin and fibrin, in the production of a sufficient clot in response to trauma, and as part of normal hemostasis. A deficiency in either factor results in an abnormal or dysfunctional clot.
2. The most common risk factor is a parent carrying the affected chromosome. In as many as one-third of patients, there may be no known family history, indicating a possible spontaneous mutation.
3. In rare cases, acquired hemophilia may occur; this is typically the result of an autoimmune response to factor VIII. Autoantibody production results in proteolytic degradation of factor VIII, more rapid plasma clearance, and subsequent bleeding complications.

C. Diagnosis

1. Obtaining a family history is critical in anticipating and making an early diagnosis.
 - a. A persistently oozing neonatal umbilical cord stump or other uncontrolled bleed early in life may indicate a bleeding disorder such as hemophilia.
 - b. The most common presentation later in life is a nontraumatic hemarthrosis in a child as he or she becomes ambulatory.
2. Patients may be classified as having mild, moderate, or severe disease according to the propensity to bleed and the circulating factor level.
3. Bleeding can occur at any site, but hemarthrosis of the elbows, knees, and ankles is the most common. Untreated or repeated joint hemarthrosis can result in a decreased range of motion and the potential for disability.

D. Treatment and Outcomes

1. Treatment includes both prophylactic and acute factor replacement.
 - a. Prophylactic factor replacement may be indicated in patients with severe disease who experience repeated atraumatic bleeds or bleeds from minor injury.
 - b. Prophylactic factor replacement should also be used in anticipation of surgery in the perioperative setting and until hemostasis has returned.
 - c. Acute factor replacement should occur in the setting of a bleed to prevent excessive bleeding and reduce morbidity and mortality. The agent and dose selected will vary according to the patient's disease state, severity of disease, any known inhibitors or other allergies, and body weight.

2. Factor replacement typically involves the use of recombinant agents, such as recombinant factor VIII or IX. Recombinant factor VIIa may be required in patients with inhibitors to factor VIII or IX, or in patients with other congenital bleeding disorders such as congenital factor VII deficiency.
3. Children with mild to moderate hemophilia A can be treated with desmopressin as an adjunctive agent. Desmopressin elevates circulating factor VIII levels by releasing bound factor VIII systemically. Caution is warranted because water intoxication, hyponatremia, and tachyphylaxis can occur.
4. Antifibrinolytics have also been used as adjunctive agents in children with hemophilia. The two commercially available agents, aminocaproic acid and tranexamic acid, help stabilize an existing clot and may be useful for procedures such as tooth extractions or dental work.
5. Patients who are given a diagnosis in infancy are appropriately treated with replacement therapy, and those who experience minimal bleeding-related episodes can achieve a life expectancy similar to their age-matched counterparts.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

Chemotherapy for infants is almost always dosed on the basis of body weight in kilograms. The rationale for this is discussed in the text. Answer A provides both drugs in milligram per kilogram values (Answer A is correct). Dosing infants by BSA will result in a relative overdose and is unwarranted. Infants have a disproportionately higher BSA relative to older children. Historical trials of children with Wilms tumor helped contribute to the understanding of this issue, in which younger, smaller children exposed to dactinomycin had untoward adverse events (e.g., SOS) when dosed by BSA instead of weight in kilograms (Answers B and D are incorrect). The traditional maximum single dose of dactinomycin is 2.5 mg; however, this would be much too high for this patient when calculated using body weight (Answer B is incorrect). Answer C is incorrect because the dose of vincristine is provided on the basis of BSA. Vincristine doses for most tumors are capped at 2 mg to prevent excess neurotoxicity; a dose of 2.5 mg would be too high for this patient (Answer D is incorrect). Doses in milligrams per square meter can be divided by a factor of 30 to produce doses in milligrams per kilogram.

2. Answer: C

Ifosfamide should always be given with hydration and mesna; hydration alone is insufficient (Answer C is correct; Answer A is incorrect). When administered as a continuous infusion, mesna should be given with ifosfamide and through at least 12 hours after the last dose, not starting after the last dose (Answer B is incorrect). Answer D uses an appropriate schedule (i.e., hours 0, 3, 6, 9, and 12), but there is no mention of hydration, which is important in preventing hemorrhagic cystitis (Answer D is incorrect).

3. Answer: C

The most appropriate answer for this case is caspofungin, according to the updated clinical practice guideline for antifungal prophylaxis in children with cancer or those receiving HSCT (Answer C is correct). Answer A is incorrect because prophylaxis is warranted. Fluconazole is no longer guideline recommended for antifungal prophylaxis in children (Answer B is incorrect). Amphotericin B is not recommended in the setting of prophylaxis (Answer D is incorrect).

4. Answer: D

Children with Down syndrome (trisomy 21) are sensitive to the toxic effects of methotrexate. As such, they should receive intermediate-dose or Capizzi-style methotrexate in lieu of high-dose methotrexate (Answers B and C are incorrect). All children with ALL should receive some intrathecal chemotherapy (Answer A is incorrect). In addition, they should be given two doses of oral leucovorin at hours 48 and 60 after a methotrexate-containing intrathecal injection during all phases of therapy except for maintenance (Answer D is correct).

5. Answer: A

Children with standard-risk ALL should receive a three-drug induction consisting of vincristine, dexamethasone, and pegaspargase (Answer A is correct; Answers C and D are incorrect; they are four-drug inductions). Dexamethasone should be used instead of prednisone because this patient is younger than 10 years and at a lower risk of osteonecrosis (Answer B is incorrect).

6. Answer: C

Treatment of high-risk neuroblastoma is aggressive and includes multiagent chemotherapy, surgery, radiation, high-dose chemotherapy with autologous stem cell rescue, and maintenance immunotherapy with aldesleukin, dinutuximab, and isotretinoin (Answer C is correct; Answers A and B are incomplete and thus incorrect). In the United States, palliative care would not be appropriate for a patient with recently diagnosed high-risk neuroblastoma receiving frontline therapy (Answer D is incorrect).

7. Answer: B

This 2-year-old patient has a stage II, favorable-histology Wilms tumor with LOH at 1p and 16q. The LOH at 1p and 16q upstages her tumor and thus necessitates receipt of DD4A (“three-drug therapy”: vincristine, dactinomycin, and doxorubicin) over EE4A (“two-drug therapy”; Answer B is correct; Answer A is incorrect). Regimens M and UH-1 would be indicated for children with higher-stage tumors and diffuse anaplasia, respectively (see Table 1 in the text; Answers C and D are incorrect).

8. Answer: A

Survivors of Wilms tumor are at high risk of developing late effects of chemotherapy, namely cardiotoxicity, secondary malignancies, and pregnancy-related complications. This patient would have received doxorubicin as part of DD4A (Answer A is correct). She would not have received irinotecan (UH-2), carboplatin (UH-1, UH-2), or etoposide (M, UH-1, UH-2; Answers B–D are incorrect).

9. Answer: A

Children with newly diagnosed osteosarcoma should receive neoadjuvant chemotherapy, followed by surgery for local control; then adjuvant chemotherapy (Answer A is correct). Osteosarcoma is considered a relatively radiation-resistant tumor (Answers B and C are incorrect). Palliative therapy would not be appropriate at this time (Answer D is incorrect).

10. Answer: A

This adolescent patient is receiving a highly emetogenic chemotherapy regimen. According to the POGO guidelines, the patient should receive aprepitant, dexamethasone, and ondansetron (Answer A is correct). Promethazine is not a guideline-supported agent (Answers B and C are incorrect). Answer D is inappropriate because aprepitant is not included in the treatment and nabilone has been removed from guideline recommendations.

11. Answer: B

A child with AML in first remission with abnormal cytogenetic features can undergo a transplant if a matched related donor is identified in a timely manner (Answer B is correct). A 10-month-old with intermediate-risk neuroblastoma should be treated with chemotherapy alone; transplantation plays no role in therapy (Answer A is incorrect). Children with sickle cell disease may be eligible for a transplant if they have an unaffected matched sibling donor (which this patient does not have; Answer C is incorrect). Children with average-risk ALL in remission after induction should continue directly to consolidation and not undergo transplantation (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

The most common malignancy in children with cancer is ALL. Mortality has decreased substantially during the past 4 decades because of the coordinated efforts of cooperative group treatment and research (Answers A and C are incorrect; Answer D is correct). Although targeted therapies have proven beneficial in selected populations (i.e., those with Ph⁺ ALL), their usefulness has not been proven in most patients with ALL (Answer B is incorrect).

2. Answer: B

The general approach to treating pediatric ALL includes induction, consolidation, and maintenance chemotherapy plus CNS prophylaxis (Answer B is correct). Several other subsets of treatment are within these major categories. The other selections include treatment approaches that apply to other pediatric malignancies (Answers A, C, and D are incorrect).

3. Answer: B

All children with newly diagnosed ALL should receive CNS prophylaxis to eradicate disease in the CNS (Answer B is correct; Answer D is incorrect). Males are at a greater risk of extramedullary (testicular) relapse than females (Answer A is incorrect). Cranial irradiation has fallen out of favor because of its undesirable effects on cognitive function; cranial irradiation and CNS chemoprophylaxis should not be used together (Answer C is incorrect).

4. Answer: A

Dexamethasone is the preferred corticosteroid for children 1–10 years of age with newly diagnosed ALL (Answer A is correct). Hydrocortisone has no role as a therapeutic corticosteroid for patients with newly diagnosed ALL (Answer B is incorrect). There is no indication that the patient cannot swallow tablets or suspension. If she were unable to swallow oral dosage forms, she would best receive intravenous dexamethasone (the preferred corticosteroid), not methylprednisolone (Answer C is incorrect). Prednisone is used in adolescents because of the increased risk of toxicity (osteonecrosis, infectious) from dexamethasone (Answer D is incorrect).

5. Answer: D

Conventional chemotherapy is the mainstay of treatment and can result in a 70%–85% OS rate (Answer D is correct). Brentuximab vedotin and crizotinib are intriguing investigational agents that have not yet been proven efficacious as frontline agents, together with conventional chemotherapy in children with ALCL. Crizotinib as a single agent showed success in patients with relapsed and refractory ALCL, but it has not been studied as a single agent for newly diagnosed ALCL (Answers A–C are incorrect).

6. Answer: A

This patient is at risk of developing cardiac dysfunction because of receiving doxorubicin and radiation (Answer A is correct). Pulmonary fibrosis is often the result of bleomycin therapy, not vincristine therapy (Answer B is incorrect). The patient is at risk of developing a secondary malignancy (caused by radiation and chemotherapy) and should be monitored closely long term for the development of another malignancy or other late effects (Answer C is incorrect). Although this patient may have impaired fertility, there is no clear evidence that a fetus born after a successful cure will be affected by the prior receipt of chemotherapy (Answer D is incorrect).

7. Answer: D

Nephrotoxicity is a hallmark adverse event associated with cisplatin and methotrexate, not vincristine. Vincristine is more commonly associated with peripheral neuropathy (Answer A is incorrect). Hemorrhagic cystitis is more commonly associated with cyclophosphamide or ifosfamide; busulfan may be more commonly associated with SOS disease or seizures (Answer B is incorrect). Anthracyclines such as doxorubicin are not commonly associated with ototoxicity; rather, they are associated with late cardiotoxicity (Answer C is incorrect). Electrolyte disturbances are a possible result of cisplatin therapy (Answer D is correct).

8. Answer: B

Routine childhood vaccinations, penicillin prophylaxis, and folic acid supplementation are important preventive measures in young children with sickle cell anemia (Answer B is correct). Vaccination and penicillin prophylaxis are well-known interventions to minimize

the risk of invasive pneumococcal disease. Folic acid supplementation is important in patients with chronic hemolysis and RBC turnover. Erythromycin should only be used in patients with a known penicillin hypersensitivity reaction (Answers A and C are incorrect). Iron supplementation should not be used because many patients with sickle cell disease will in fact have iron overload because of transfusion therapy (Answer D is incorrect). Vitamin B₁₂ supplementation has no routine role in the treatment of sickle cell disease (Answer C is incorrect).

9. Answer: A

Oral hydroxyurea therapy should be considered for this patient to minimize the complications of her disease and help prevent hospitalizations (Answer A is correct). The other options are not appropriate for this patient because there is no indication that she is yet in need of chelation (i.e., no history of transfusions to date; Answer B is incorrect), she has no HLA-matched donor available (both siblings have sickle cell disease; Answer C is incorrect), and she has no indication yet for chronic RBC transfusions (i.e., no known history of stroke; Answer D is incorrect).

10. Answer: B

Dactylitis is a common presenting symptom in children with sickle cell disease. Dactylitis can be caused by infection with *Salmonella* or *Staphylococcus* spp.; a patient with sickle cell disease presenting with fever and symptoms of dactylitis should receive antibiotics that cover these organisms (Answer B is correct; Answer D is incorrect). *Streptococcus*, a potentially infectious organism in children with sickle cell disease, is not one of the top infectious organisms in the setting of dactylitis (Answer C is incorrect). *Enterococcus* would not normally be a causative infectious organism for dactylitis (Answer A is incorrect).

11. Answer: C

Oral deferasirox can be used in children at least 2 years of age for chronic transfusion-related iron overload (Answer C is correct). Iron chelation should be considered when the patient has received about 120 mL/kg of packed RBCs (Answer A is incorrect). Deferiprone is only indicated in adults (Answer B is incorrect). Deferoxamine can be used for both acute and chronic iron overload (Answer D is incorrect).

12. Answer: C

This patient has a known history of hemophilia but has no available medical records and is unconscious and critically bleeding. The type of hemophilia and the presence of inhibitors are unknown. The medical team will be using blood products, but the team is also asking about a pharmacologic option. Recombinant factor VIIa would be most appropriate from the selections provided (Answer C is correct). Waiting for laboratory analysis could delay control of the bleeding, which could worsen the patient's clinical presentation (Answer A is incorrect). Recombinant factor VIII might not currently be best because the patient may have another type of hemophilia, such as hemophilia B (which would require factor IX) or hemophilia A or B with inhibitors (which would most benefit from factor VIIa; Answer B is incorrect). Factor IX is only effective for hemophilia B, not hemophilia A (Answer D is incorrect).

SOLID ORGAN TRANSPLANTATION

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Learning Objectives

1. Examine how current strategies used to prevent and treat solid organ transplantation (SOT) rejection affect cellular and antibody-mediated immune responses.
2. Compare therapeutic effects, drug interactions, monitoring, and safety of current immunosuppressants used in SOT.
3. Determine the therapeutic goals for individual SOT recipients with respect to balancing preventing rejection and avoiding infections and other complications.
4. Differentiate how recommended immunizations for pre-SOT candidates and SOT recipients vary from U.S. recommendations for immunocompetent pediatric patients.
5. Describe preventive and treatment strategies for pediatric SOT complications, including infection, malignancy, linear growth impairment, post-transplant diabetes mellitus, and cardiovascular complications.

Abbreviations in This Chapter

aHUS	Atypical hemolytic uremic syndrome
AMR	Antibody-mediated rejection
ATG	Antithymocyte globulin
AUC	Area under the curve
CCS	Corticosteroid
CMV	Cytomegalovirus
CNI	Calcineurin inhibitor
CYP	Cytochrome P450
DSA	Donor-specific antibody
eATG	Equine antithymocyte
EBV	Epstein-Barr virus
ESRD	End-stage renal disease
FKBP12	FK506 binding protein
HLA	Human leukocyte antigen
HUS	Hemolytic uremic syndrome
IVIG	Intravenous immunoglobulin
KDIGO	Kidney Disease: Improving Global Outcomes
mTOR	Mammalian target of rapamycin
NK	Natural killer
NTI	Narrow therapeutic index
PCR	Polymerase chain reaction
PRA	Panel of reactive antibody

PTDM	Posttransplant diabetes mellitus
PTLD	Posttransplant lymphoproliferative disorder
PyVAN	Polyomavirus-associated nephropathy
REMS	Risk Evaluation and Mitigation Strategies
rATG	Rabbit antithymocyte globulin
SCr	Serum creatinine
SOT	Solid organ transplantation
TDM	Therapeutic drug monitoring
WBC	White blood cell count

Self-Assessment Questions

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

1. M.M. is a 15-year-old female patient (weight 50 kg, height 150 cm) who received a deceased donor kidney transplant 2 months ago for end-stage renal disease (ESRD) caused by polycystic kidney disease. At transplantation, she received four doses of rabbit antithymocyte globulin (rATG; Thymoglobulin) 75 mg intravenously for induction. Her maintenance immunosuppressive regimen includes tacrolimus 3 mg by mouth twice daily, mycophenolate mofetil 500 mg by mouth twice daily, and prednisone 15 mg by mouth daily. Her 12-hour tacrolimus trough concentration this morning was 6.3 ng/mL, which was obtained appropriately. M.M.'s tacrolimus trough concentrations were 9.6 ng/mL and 8.9 ng/mL 2 weeks and 1 week ago, respectively. The patient has had no changes in her tacrolimus dose for 3 weeks. The patient's target trough concentration goal is 8–10 ng/mL. Which factor most likely contributed to M.M.'s subtherapeutic tacrolimus trough concentration?
 - A. M.M. started amlodipine 5 mg by mouth daily 1 week ago for hypertension.
 - B. M.M. started high school 4 days ago and is now taking her medication doses with breakfast and dinner, compared with on an empty stomach previously.
 - C. M.M. vomited 30 minutes after taking her morning medications (including tacrolimus) 5 days ago and did not take medications again that until the evening dosing time.
 - D. M.M. started atorvastatin 10 mg by mouth daily 1 week ago for hyperlipidemia.

2. E.G. is an 11-year-old female heart transplant candidate with congestive heart failure. On review of her chart, it was noted that E.G. has documented allergies to acetaminophen and diphenhydramine (urticaria). The heart transplant team would like to use an induction agent that would not require premedication in order to avoid acetaminophen and diphenhydramine. Which best depicts the biologic agent used in pediatric transplantation that is typically administered without premedications (acetaminophen, a corticosteroid [CCS], and/or an antihistamine)?
- Basiliximab
 - Alemtuzumab
 - rATG
 - Rituximab
3. K.G. is a 13-year-old African American female patient (weight 50 kg, height 155 cm) with ESRD caused by immunoglobulin (Ig)A nephropathy who is postoperative day 3 from a deceased donor kidney transplant. She received two doses of rATG 75 mg intravenously for transplant induction. K.G. will receive a third dose of rATG today. How should the dose of rATG be adjusted if the patient's white blood cell count (WBC) is 3×10^3 cells/mm³ and her platelet count is 40,000/mm³?
- No change is necessary; administer rATG 75 mg intravenously.
 - Hold rATG dose.
 - Administer rATG 50 mg intravenously.
 - Administer rATG 25 mg intravenously.

Questions 4 and 5 pertain to the following case.

P.M. is a 16-year-old white female patient who received a bilateral lung transplant for end-stage lung disease caused by pulmonary arterial hypertension 3 months ago. P.M. is being seen in the lung transplant clinic today, and her current immunosuppressive regimen includes tacrolimus 1.5 mg by mouth twice daily, mycophenolate sodium (Myfortic) 720 mg by mouth twice daily, and prednisone 15 mg by mouth once daily. P.M. has been on a stable dose of tacrolimus for the past month, and her tacrolimus trough concentration this morning was at goal. The patient had also been receiving voriconazole 200 mg orally twice daily for *Aspergillus* spp. prophylaxis,

but today, the transplant pulmonologist wants to discontinue this medication because of the patient's elevated liver function test results.

4. Which would be the best adjustment for P.M.'s tacrolimus dose?
- Decrease to tacrolimus 0.5 mg orally twice daily with a follow-up trough tacrolimus concentration in 3 days.
 - Increase to tacrolimus 4.5 mg orally twice daily with a follow-up trough tacrolimus concentration in 3 days.
 - No adjustment is necessary; follow up on trough tacrolimus concentration in 3 days.
 - Increase tacrolimus 3 mg orally twice daily with a follow-up trough tacrolimus concentration in 3 days.
5. P.M. is currently receiving mycophenolate sodium. Which set of adverse effects is most commonly associated with mycophenolate formulations?
- Delayed wound healing and hyperlipidemia
 - Pancytopenia and nephrotoxicity
 - Gastrointestinal (GI) toxicity and pancytopenia
 - Hyperglycemia and neurotoxicity

Questions 6 and 7 pertain to the following case.

B.B. is a 13-year-old female patient who received a deceased donor heart transplant 6 months ago because of congenital heart disease. She is currently intubated in the pediatric intensive care unit for suspected pneumonia and cannot take oral medications. Her home dose of cyclosporine-modified capsules (Neoral) is 100 mg orally twice daily. She has had no changes in interacting medications, and the transplant cardiologist would like to convert her to continuous-infusion intravenous cyclosporine.

6. Which would be the best infusion rate to prescribe?
- 1.4 mg/hour
 - 2.8 mg/hour
 - 6.3 mg/hour
 - 8.3 mg/hour

7. Because of B.B.'s history, there is concern for candidemia. Which best reflects the antifungal agent with the least potential for adverse drug reactions or drug-drug interactions in combination with cyclosporine modified?
- Itraconazole
 - Amphotericin B
 - Voriconazole
 - Micafungin
8. D.R., a 9-year-old African American female patient who presents after a liver transplant 8 years ago caused by biliary atresia, is admitted to the hospital with scleral icterus, elevated transaminases, and elevated total bilirubin. After the patient undergoes a liver biopsy, she is given a diagnosis of severe acute cellular rejection, likely because of medication nonadherence. It is decided to treat D.R. with intravenous rATG. She will continue her maintenance medications of tacrolimus and low-dose prednisone. D.R. will also be initiated on mycophenolate mofetil, valganciclovir, and sulfamethoxazole/trimethoprim. Which drug most commonly requires routine TDM?
- Tacrolimus
 - Valganciclovir
 - Mycophenolate mofetil
 - rATG
9. A.A. is a 5-year-old Asian female patient with end-stage liver disease caused by Alagille syndrome who was admitted to the hospital today for a deceased donor liver transplant. Which maintenance immunosuppressive regimen would be best for A.A. after transplantation?
- Immediate-release tacrolimus (Prograf) and CCS
 - Belatacept, mycophenolate mofetil, and CCS
 - Sirolimus, tacrolimus, and CCS
 - Extended-release, once-daily tacrolimus (Astagraf) and CCS
10. J.M. is a 4-year-old Hispanic female patient with ESRD caused by recently confirmed atypical hemolytic uremic syndrome (aHUS) due to complement factor H mutation, although she has been on chronic hemodialysis for the past 6 months. The pediatric hematologist and nephrologist decided today that, although J.M. would unlikely regain renal function with initiation of eculizumab, C5 inhibition would protect her from further renal injury and injury to other organ systems. J.M. is also being seen in the clinic today for a pharmacotherapy pre-kidney transplant evaluation before starting eculizumab. Which would be most important before initiating chronic therapy with eculizumab?
- The prescribers should be informed that supplemental doses of eculizumab are not required after plasmapheresis or plasma exchange.
 - The prescribers should be informed that supplemental doses of eculizumab are recommended after hemodialysis.
 - Before administering eculizumab, the facility administering eculizumab must enroll in the eculizumab Risk Evaluation and Mitigation Strategy (REMS) program.
 - J.M. should receive the quadrivalent meningococcal conjugate vaccine at least 2 weeks before treatment with eculizumab.
11. J.P. is a 17-year-old male patient with a history of renal transplantation 3 months ago due to ESRD caused by dysplastic kidneys. J.P.'s current immunosuppressive regimen consists of tacrolimus 6 mg by mouth twice daily, mycophenolate mofetil 1000 mg by mouth twice daily, and prednisone 7.5 mg by mouth daily. Tacrolimus trough concentration was 10.1 ng/mL 2 weeks ago and is 14.4 ng/mL today. The patient's current anti-infection regimen consists of valganciclovir 900 mg by mouth daily, sulfamethoxazole/trimethoprim 800–160 mg by mouth three times weekly, and fluconazole 100 mg by mouth daily. The patient's serum creatinine (SCr) has been stable at 0.7–0.8 mg/dL. Two weeks ago, J.P.'s blood BK virus polymerase chain reaction (PCR) was 1790 copies, and from the most recent laboratory results this week, his blood BK virus PCR was positive at 10100 copies/mL. J.P. is given a diagnosis of presumptive BK polyomavirus-associated nephropathy (PyVAN). According to the 2013 American Society of Transplantation infectious disease guidelines, which strategy would be best to treat BK PyVAN?

- A. Reduce immunosuppression.
 - B. Give cidofovir.
 - C. Give leflunomide.
 - D. Give valganciclovir.
12. A.V. is a 26-month-old Hispanic male patient who received a heart transplant for severe dilated cardiomyopathy yesterday evening. A.V. received induction with basiliximab. The patient is considered at high risk of cytomegalovirus (CMV) disease because the transplant donor was CMV IgG positive and the recipient was CMV IgG negative at transplantation. Which best depicts the guideline-based strategy for CMV prophylaxis for A.V.?
- A. Intravenous ganciclovir, followed by conversion to oral valganciclovir when A.V. is considered stable.
 - B. CMV intravenous immunoglobulin (IVIG) (Cytogam).
 - C. Intravenous acyclovir, followed by conversion to oral acyclovir when A.V. is considered stable.
 - D. Intravenous cidofovir, followed by conversion to oral brincidofovir when A.V. is considered stable.
13. Z.C. is 9-year-old white female patient after a liver transplant 8 years ago for biliary atresia. She has had several posttransplant complications, including chronic rejection and posttransplant lymphoproliferative disorder (PTLD). Z.C.'s immunosuppressive regimen is currently tacrolimus 1.5 mg by mouth twice daily, sirolimus 1.5 mg by mouth daily, and prednisolone 4 mg by mouth daily. Which most appropriately represents the factor that would increase Z.C.'s risk of posttransplant diabetes mellitus (PTDM)?
- A. Biliary atresia
 - B. Ethnicity
 - C. Age at transplantation
 - D. Tacrolimus use

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.5
3. Domain 3: Information Management, Research, and Education; Task(s): 3.2, 3.4, 3.5
4. Domain 4: Public Health and Patient Advocacy; Task(s): 4.3

I. HISTORY

- A. Solid Organ Transplantation (SOT) – Has been successfully performed in humans in the United States since 1954.
- B. Bone Marrow/Stem Cell Transplantation – Please see the Hematology/Oncology chapter.

II. ORGANS TRANSPLANTED AND SURVIVAL RATES

Table 1. Pediatric Organ Transplants Performed in the United States in 2021 (< 18 years of age)

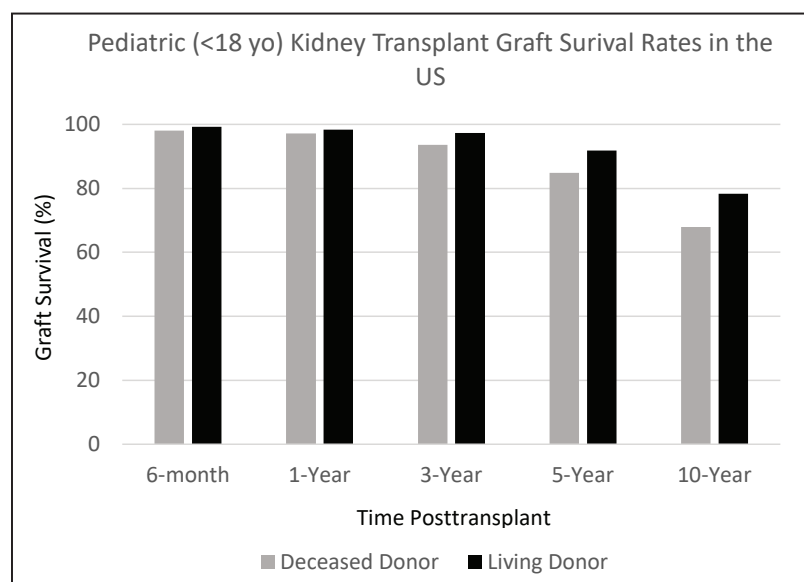
	Overall ^a	Kidney	Liver	Heart	Lung	Intestine
< 1 year old (yo)	257	0	139	111	5	1
1–5 yo	511	184	186	106	2	19
6–10 yo	288	138	63	67	4	11
11–17 yo	834	497	113	204	12	5
All pediatric transplants	1890	819	501	488	23	36

^aIncludes kidney/pancreas, heart/lung, and pancreas.

Adapted from: Transplants in the U.S. by Recipient Age. Organ Procurement and Transplantation Network Web site. Available at <https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/>.

- A. Deceased Donor Transplantation: Deceased donors for liver, kidney, heart, intestine, and lung
- B. Living Donor Transplantation: Living donation for liver, kidney, and lung with reports of intestine and heart living donation

III. SURVIVAL



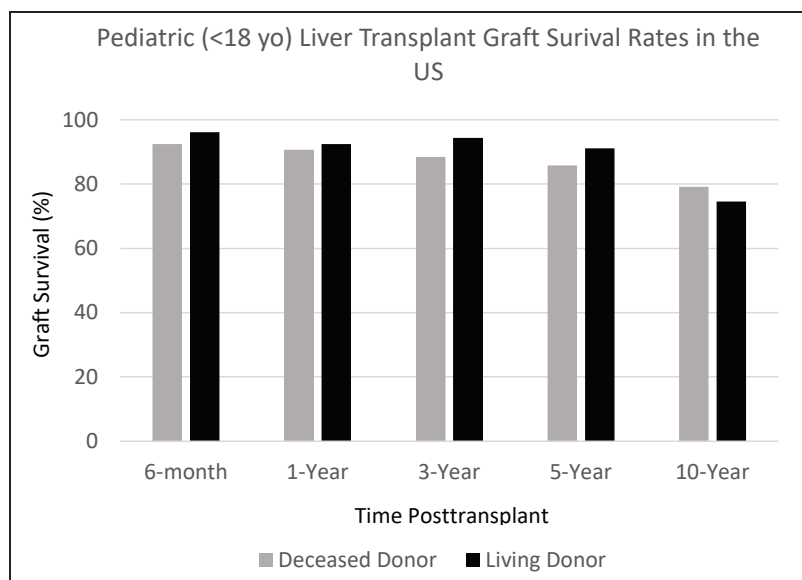


Figure 1. Pediatric kidney and liver transplant graft survival rates in the United States (2020).

Adapted from: OPTN/SRTR Annual Data Report 2020. Am J Transplant 2022;22(suppl 2):1-647.

IV. INDICATIONS FOR SOLID ORGAN TRANSPLANTATION

- A. Restorative Treatment for End-Stage Organ Disease
- B. Prevalence of Transplants Increasing with:
 1. Improved surgical techniques
 2. Immunosuppressive regimens
 3. Disease state management leading up to transplantation
- C. Kidney: Most Common Causes of ESRD in Pediatric Patients
 1. Focal segmental glomerulosclerosis: May recur in transplanted kidney
 2. Aplasia, hyperplasia, and dysplasia
 3. Obstructive uropathy
 4. Reflux nephropathy
 5. Systemic lupus erythematosus nephritis
 6. Hemolytic uremic syndrome (HUS)
 - a. Atypical hemolytic uremic syndrome (aHUS) may recur in transplanted kidney.
 - b. Eculizumab and ravulizumab have effectively prevented and treated recurrent aHUS disease in pediatric kidney transplant recipients (see section XVII for further detail).
 7. Chronic glomerulonephritis: Dense deposit disease and C3 glomerulonephritis may recur in transplanted kidney.
 8. Polycystic kidney disease
 9. Congenital nephrotic syndrome
 10. Prune belly syndrome

- D. Liver: Most common causes of end-stage liver disease in pediatric patients
 - 1. Cholestatic liver disorders, including, but not limited to:
 - a. Biliary atresia (most common cause of pediatric end-stage liver disease)
 - b. Primary sclerosing cholangitis
 - c. Alagille syndrome
 - 2. Fulminant hepatic failure
 - 3. Metabolic liver disease, including, but not limited to:
 - a. α_1 -Antitrypsin deficiency
 - b. Tyrosinemia
 - c. Cystic fibrosis
 - d. Wilson disease
 - 4. Cryptogenic cirrhosis
 - 5. Liver tumors
 - 6. Autoimmune hepatitis
- E. Heart: Most common indications for cardiac transplantation in pediatric patients
 - 1. Intractable heart failure
 - 2. Congenital heart disease
 - 3. Unresectable malignant cardiac tumors
- F. Lung: Most common indications for lung transplantation in pediatric patients
 - 1. Cystic fibrosis (indication for around 60% of pediatric lung transplants)
 - 2. Pulmonary hypertension
 - 3. Obliterative bronchiolitis
 - 4. Interstitial lung disease
 - 5. Congenital heart disease
- G. Intestine: Indications for intestine transplantation (isolated intestine transplantation typically used when parenteral nutrition contraindicated or inadequate)
 - 1. Short gut syndrome: Volvulus, gastroschisis, necrotizing enterocolitis, atresia
 - 2. Motility disorders
 - 3. Mucosal defects

V. PRETRANSPLANT EVALUATION

- A. ABO Compatibility
 - 1. Based on blood typing, with concepts similar to blood donation.
 - a. O is the universal donor.
 - b. AB blood type is the universal recipient.
 - 2. Transplantation typically contraindicated if recipient and donor have incompatible blood groups. High risk of hyperacute rejection (inflammatory response by immune system leading to graft dysfunction and possible loss, typically within 24 hours of transplantation) owing to anti-A and anti-B antibodies.
 - 3. Some transplant centers have successfully performed ABO-incompatible transplants for kidney, liver, intestine, lung, and heart transplants because of the limited organ supply and high wait list mortality for specific organs and disease states.
 - a. May use strategies including plasma exchange, IVIG, rituximab, and/or splenectomy.
 - b. Younger children, particularly those younger than 24 months, may have increased success with ABO-incompatible transplantation because of their relatively immature immune system.

B. Panel of Reactive Antibody (PRA)

1. PRA is a marker of a potential organ recipient's anti-human leukocyte antigen (HLA) antibodies (class I and class II).
2. PRA is rated on a scale of 0%-100%, with a higher PRA often resulting in a decreased likelihood of finding a suitable organ.
3. Patients with elevated PRA are considered "sensitized" and at increased risk of acute rejection for kidney, heart, intestine, and lung transplantation.
 - a. Acute rejection: Intense inflammatory response isolated within the donated organ primarily caused by lymphocytes interacting with donor alloantigens, often within the first 3 months of transplantation.
 - b. Lymphocyte-depleting agents are often used as induction agents for highly sensitized transplant recipients unless there is a contraindication (see section X).

C. Crossmatch

1. Patient serum is tested against donor lymphocytes to detect preformed antibodies versus the donor HLA.
2. A positive crossmatch is often thought to be a contraindication for kidney, heart, intestine, and lung transplantation, although some transplant programs still transplant with a positive crossmatch and adjust immunosuppressive regimen accordingly.
3. Factors that increase the chance of a positive crossmatch include:
 - a. Blood transfusion
 - b. Pregnancy
 - c. Retransplantation

D. HLA Tissue Typing

1. HLA, the human version of the major histocompatibility complex, is encoded on chromosome 6 in humans. Each person receives one set of antigens from each parent.
2. Tissue typing helps determine the suitability of the match for donor and recipient.
 - a. According to the United Network for Organ Sharing, both pairs of HLA-A, HLA-B, and HLA-DR must be specifically assessed for pre-SOT. For example, a recipient and donor who share HLA-A2 and HLA-DR52, but no other HLA matches, would be considered a four of six HLA mismatch (1 HLA-A, 2 HLA-B, 1 HLA-DR).
 - b. HLA-C, HLA-DQ, HLA-DP are also often assessed

E. Evaluation of Suitability as a Surgery Candidate and as a Posttransplant Candidate by Various Services:

1. Detailed process guided by transplant governing bodies.
2. Contains specific role for the pediatric transplant pharmacist.

VI. SURGICAL SOLID ORGAN TRANSPLANTATION PROCEDURE**A. Kidney Transplantation**

1. Typically, solitary transplanted kidney is placed in the abdomen of the recipient.
2. Some patients may require a pretransplant nephrectomy or nephrectomy of native kidney(s) at transplantation, primarily for drug-resistant proteinuria, refractory hypertension, or chronic renal parenchymal infection.
3. Fluid balance is essential posttransplantation because transplanted kidneys, especially adult transplanted kidneys in small children, require a large proportion of cardiac output. 1 mL of replacement fluid per 1 mL of urine output may be required with continuous intravenous fluids in the immediate postoperative phase.

- B. Liver Transplantation: The whole transplanted liver (or segmental graft) is placed in the abdomen of the recipient, with complete removal of the recipient's native liver.
- C. Heart Transplantation
 - 1. Placement of donor heart after removal of recipient's heart.
 - 2. Patient size, location of heart, and cardiac anatomy are all considered for surgery.
- D. Lung Transplantation
 - 1. Because of indications for pediatric lung transplantation, bilateral sequential lung transplantation, in which each donor lung is implanted separately with the removal of the recipient's diseased lung, is most common. Single-lung transplantation in pediatric patients is rare.
 - 2. Cardiopulmonary bypass is often used for pediatric lung transplantation.
- E. Intestine Transplantation
 - 1. Isolated intestine transplantation: Small intestine alone transplanted with donor superior mesenteric artery, which is anastomosed to recipient aorta or superior mesenteric artery.
 - 2. Composite liver-intestine: Often includes duodenum and head of pancreas.
 - 3. Multivisceral: May include any combination of abdominal organs with the small intestine.

VII. T-CELL SIGNALING AND REPLICATION

- A. T-Cell Signals Fall into the Following 3
 - 1. Signal 1 (Recognize)
 - a. Antigen-presenting cells, including macrophages, B cells, and dendritic cells, display antigen to CD4⁺ T cells through the major histocompatibility complex.
 - b. Antigen binds to the T-cell receptor, causing activation of the T cell.
 - c. Inevitably leads to increased production of interleukin (IL)-2, which is a growth factor responsible for T-cell up-regulation.
 - 2. Signal 2 (Verify)
 - a. The antigen-presenting cell also binds to the T cell through CD80 and CD86 interaction with CD28.
 - i. Both CD80 and CD86 can bind with CD28 to regulate T-cell clonal expansion and differentiation.
 - ii. When CD80 and CD86 bind with cytotoxic T-lymphocyte antigen-4 (CTLA-4), also known as CD152, T-cell activation and proliferation are inhibited, leading to anergy or apoptosis. CTLA-4 is only expressed during T-cell activation.
 - b. This process is called co-stimulation.
 - c. This process is required for T-cell proliferation.
 - 3. Signal 3 (Activate and proliferate)
 - a. IL-2 binds to CD25, also known as the IL-2 receptor.
 - b. Stimulates mammalian target of rapamycin (mTOR).
 - c. Leads to stimulation of cell cycle.
 - d. Concurrently, purine synthesis occurs through inosine monophosphate dehydrogenase.
 - e. This leads to mRNA (messenger RNA) translation and protein synthesis, which in turn leads to T-cell proliferation.

- B. T-Cell Activation Leads to Effector Responses Mediated by Various Cell Types.
 - 1. CD8+ cytotoxic T cells
 - 2. T-cell mediated delayed-type hypersensitivity cells
 - 3. B cells
 - 4. Memory T cells

VIII. IMMUNOBIOLOGY OF SOLID ORGAN TRANSPLANT REJECTION

- A. Rejection: Inflammatory response by immune system leading to graft dysfunction and loss
- B. Definitions
 - 1. Humoral rejection
 - a. Also known as
 - i. Antibody-mediated rejection (AMR)
 - ii. Acute vascular rejection
 - b. Implicated cells: B cells, antibodies, complement, platelets, coagulation factors
 - c. Involvement in rejection
 - i. Hyperacute rejection: Involves preexisting antibodies.
 - ii. Acute rejection: Involves antibodies formed against donor organ after transplantation.
 - iii. Chronic rejection: Involves development of antidonor antibodies.
 - 2. Cellular rejection
 - a. Implicated cells and factors
 - i. T cells
 - (a) Helper T cells (CD4⁺) most common.
 - (b) Cytotoxic T cells (CD8⁺)
 - ii. Antigen-presenting cells: Macrophages, dendritic cells, B cells
 - iii. Cytokines
 - iv. Adhesion molecules
 - v. Natural killer (NK) cells
 - b. Involvement in rejection: T cells are the primary mediator for acute cellular rejection.

IX. TYPES OF REJECTION

- A. Hyperacute
 - 1. Definition: Recipient has preexisting antibodies to donor antigens from prior sensitizations. Increased risk of sensitization: Blood transfusions, prior pregnancies, retransplantation
 - 2. Classification: Primarily AMR from preexisting antibodies
 - 3. Timing
 - a. Typically occurs within first 24 hours of transplantation.
 - b. Onset can occur within minutes of reperfusion of transplanted organ.
 - 4. Result
 - a. Interstitial hemorrhage
 - b. Necrosis of vasculature and loss of graft
 - 5. Prevention: Blood typing and crossmatch before transplantation

B. Acute

1. Definition: Intense inflammatory response isolated within transplanted organ primarily caused by T-cells interacting with donor antigens
2. Classification
 - a. Primary: Cellular rejection
 - b. Secondary: Humoral, as antibodies form against donor antigens.
 - c. Timing: Usually occurs within first 90 days after transplantation.
 - d. Result
 - i. Signs/symptoms: Redness or edema at incision site, fever, pain, and decreased graft function
 - (a) Kidney transplantation: Decreased graft function – increasing SCr, blood urea nitrogen (BUN)
 - (b) Liver transplantation: Decreased graft function – increasing liver enzymes or bilirubin and/or jaundice
 - (c) Heart transplantation: Decreased graft function – increasing brain natriuretic peptide or N-terminal pro-brain natriuretic peptide – in severe cases, hemodynamic compromise
 - (d) Lung transplantation: Decreased graft function – worsening pulmonary function tests, chills, shortness of breath, cough, chest tightness
 - (e) Intestine transplantation: Can be asymptomatic, or decreased graft function – diarrhea, increased stoma output, obstruction, or bleeding
 - ii. Graft injury and dysfunction
 - iii. Increased risk of chronic rejection
 - e. Diagnosed often with biopsy of transplanted organ(s). In kidney transplants, the following criteria are used to diagnose acute AMR:
 - i. Positive C4d stain in the peritubular capillaries on biopsy
 - ii. Histologic changes on biopsy that are consistent with AMR
 - iii. Presence of HLA donor-specific antibodies (DSA): Tested using the Luminex assay from blood samples, not from the biopsy sample. There may also be a role for non-HLA antibodies in acute AMR without HLA DSA (e.g., angiotensin II type 1 receptor antibody and endothelin-1 type A receptor antibody).
 - f. Prevention: Induction immunosuppression and adherence to maintenance immunosuppressive regimen after transplantation

C. Chronic

1. Definition: Slow, progressive immune and inflammatory response to graft over time
 - a. Causes scarring and dysfunction of graft.
 - b. Major cause of late graft loss
2. Timing: Slow and insidious
3. Result: Graft injury, graft dysfunction, graft loss
4. Presents differently for different organ types
 - a. Renal transplantation: CAN/IFTA (Chronic Allograft Nephropathy/Interstitial Fibrosis and Tubular Atrophy)
 - b. Liver transplantation: Cholestasis, arterial injury, and vanishing bile ducts/ductopenia (on biopsy)
 - c. Heart transplantation: Chronic allograft vasculopathy – Intimal proliferation of coronary arteries
 - d. Lung transplantation: Chronic lung allograft dysfunction – Progressive decline in FEV₁ (forced expiratory volume in 1 second)
 - e. Intestine transplantation: Intimal hyperplasia and obliterative arteriopathy

X. IMMUNOSUPPRESSIVE THERAPY**A. Goals**

1. Induce immunologic tolerance – Ultimate goal, involving discontinuation of antirejection medications, though rarely successfully achieved.
2. Maintain low incidence of acute rejection.
3. Improve long-term allograft survival.
4. Limit opportunistic infections.
5. Avoid malignancy.
6. Minimize adverse effects of medications.

B. Types of Immunosuppression

1. Maintenance: Oral or intravenous medications given after induction phase to prevent acute rejection while minimizing drug-related toxicity
2. Induction: Potent intravenous (or subcutaneous in particular cases) immunosuppression at transplantation
3. Rescue: Used to treat acute rejection

C. Maintenance Therapy

1. Antiproliferative agents
 - a. Mycophenolate mofetil/mycophenolate sodium
 - b. Azathioprine
2. Calcineurin inhibitors (CNIs)
 - a. Tacrolimus
 - b. Cyclosporine
3. Corticosteroids (CCS)
4. Most common regimen in the United States is tacrolimus plus mycophenolate mofetil/mycophenolate sodium with or without CCS.
5. Other agents/strategies
 - a. mTOR inhibitors (sirolimus and everolimus)
 - b. Calcineurin-sparing
 - c. Steroid-sparing
 - d. Selective T-cell co-stimulation blocker (belatacept)

D. Induction Therapy

1. Potent perioperative immunosuppression
 - a. Lymphocyte-depleting agents
 - i. Antithymocyte globulin (ATG) – Polyclonal
 - (a) Rabbit – rATG (Thymoglobulin)
 - (b) Equine antithymocyte globulin (eATG) – ATGAM
 - ii. Alemtuzumab (Campath) – Monoclonal
 - b. Non-lymphocyte-depleting agent
 - i. Basiliximab (Simulect) – Monoclonal
2. Purpose
 - a. Potentially decrease rejection, depending on organ type.
 - i. Protocol driven by different hospitals.
 - ii. Choice of agent, and whether to use an induction agent, often depends on several factors, including, but not limited to, whether the patient is sensitized before transplantation, whether the patient is having a retransplant, whether there is recent infection, or whether steroids will be avoided, rapidly withdrawn, or minimized.

- b. Decrease rates of delayed graft function.
- c. Induce tolerance or “prope” (near) tolerance: Recipient conditioned to develop immunologic hypo-responsiveness to donor antigen.
- d. Advantages versus disadvantages

Table 2. Advantages vs. Disadvantages of Induction Therapy

Advantages	Disadvantages
• Simpler regimen ○ Improved adherence ○ Reduced pill burden • Potentially avoid/minimize adverse drug effects of calcineurin inhibitors and/or steroids • Decrease risk of early rejection	• Infusion-related reactions with lymphocyte-depleting agents ○ “Flu-like” syndrome ○ Premedications required • With lymphocyte-depleting agents: Leukopenia, thrombocytopenia, increased infection susceptibility, potential increased risk of malignancy • Cost (except alemtuzumab)

3. Organ-specific guidelines/consensus statements
 - a. Kidney – Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (2009)
 - i. Includes limited pediatric data; thus, recommendations should be used cautiously in the pediatric population.
 - ii. Basiliximab is the recommended agent for patients who are not considered high immunologic risk.
 - iii. Suggest using ATG for kidney transplant recipients at high risk of acute rejection; risk factors that factor into a patient’s being at high risk of acute rejection include:
 - (a) Increased number of HLA mismatches
 - (b) Young recipient age
 - (c) Older donor age
 - (d) African American recipient
 - (e) ABO incompatibility
 - (f) Delayed onset of kidney function
 - (g) Cold ischemic time greater than 24 hours
 - (h) PRA greater than 0%
 - (i) Presence of DSA
 - b. Liver – Long-Term Medical Management of the Pediatric Patient After Liver Transplantation: 2013 Practice Guideline by the American Association for the Study of Liver Diseases (AASLD) and the American Society of Transplantation (AST). No specific recommendations whether to use induction or, if so, which agent to use. In addition, although the AASLD guidelines do not recommend specific maintenance immunosuppressive regimens, these guidelines note tacrolimus-based regimens have lower rates of rejection.
 - c. Heart – The International Society for Heart and Lung Transplantation (ISHLT) Guidelines for the Care of Heart Transplant Recipients (2010)
 - i. Both adult and pediatric specific recommendations included.
 - ii. Outlines that routine use of empiric induction therapy is not superior to regimens that do not include induction therapy (adult and pediatric recommendation)
 - iii. Induction, combined with maintenance regimen of tacrolimus, CCS, and mycophenolate mofetil or mTOR inhibitor, indicated when recipient has pre-formed DSA and positive transplant crossmatch.

- iv. ATG indicated when:
 - (a) Complete steroid avoidance is planned (pediatric specific recommendation).
 - (b) Recipient at high risk of acute rejection (pediatric and adult recommendation).
 - (c) It may be beneficial to delay/avoid CNIs because of renal dysfunction concerns (pediatric and adult recommendation).
 - d. Lung: AST Executive Summary on Pediatric Lung Transplantation (2007) – No consensus whether induction indicated at time of lung transplantation.
- E. Rescue
- 1. Treatment of acute cellular rejection
 - a. Dependent on several factors, including, but not limited to, specific transplant center guidelines, severity of cellular rejection, type of transplantation, and patient-specific factors.
 - b. Kidney – KDIGO guidelines
 - i. Recommend CCS, typically starting with intravenous CCS, for the initial treatment of acute cellular rejection.
 - ii. Suggest lymphocyte-depleting agent (e.g., ATG) for acute cellular rejection that is unresponsive to treatment with CCS or for recurrent acute cellular rejection.
 - c. Liver – AASLD/AST guidelines: Most liver transplant recipients respond to intravenous CCS, increased CNI exposure, and/or addition of antiproliferative agent.
 - d. Heart – ISHLT guidelines
 - i. Symptomatic acute cellular rejection (pediatric and adult recommendations)
 - (a) High-dose intravenous CCS are first line with adjustment of maintenance immunosuppressive regimen.
 - (b) ATG should be added to high-dose intravenous CCS if there is hemodynamic compromise or no improvement within 12–24 hours of CCS initiation with adjustment of maintenance immunosuppressive regimen.
 - ii. Asymptomatic acute cellular rejection (pediatric and adult recommendations)
 - (a) Severe: High-dose intravenous CCS with adjustment of maintenance immunosuppressive regimen. ATG may be considered if no histologic resolution.
 - (b) Moderate: Intravenous or oral CCS with adjustment of immunosuppressive regimen
 - (1) ATG may be considered if no histologic resolution
 - (2) If more than 12 months after transplant, may not require treatment
 - (c) Mild: Treatment often not required
 - iii. Recurrent or CCS-resistant acute cellular rejection (pediatric and adult recommendations)
 - (a) Consider ATG.
 - (b) Additional approaches include methotrexate, photopheresis, and total lymphoid irradiation.
 - e. Lung – AST executive summary
 - i. Pulse CCS suggested as initial therapy
 - ii. Persistent acute cellular rejection usually responds to monoclonal or polyclonal T-cell antibody therapy (e.g., ATG).
 - 2. Treatment of acute AMR
 - a. Dependent on several factors, including, but not limited to, specific transplant center guidelines, severity of cellular rejection, type of transplantation, and patient-specific factors
 - b. Kidney – KDIGO guidelines (the Transplantation Society published guidelines in 2020, but pediatric recipients were not specifically addressed [Transplantation 2020;104:911–922]) – Suggest one or a combination of the following to treat acute AMR with or without a CCS:
 - i. Plasmapheresis
 - ii. IVIG
 - iii. Rituximab
 - iv. Lymphocyte-depleting agent (e.g., ATG)

- c. Heart – ISHLT guidelines – Suggest a combination of the following strategies (adult and pediatric recommendation):
 - i. Intravenous CCS or ATG to reduce immune-mediated injury
 - ii. IVIG, plasmapheresis, and/or immune apheresis
 - iii. May consider adjusting maintenance immunosuppressive regimen
 - iv. Also, in particular cases, bortezomib, carfilzomib, and eculizumab have been used, though they are not recommended in the guidelines
 - d. Lung – Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation (2016) Highlights that most experts would treat pediatric lung transplant recipients with all of the following criteria: Antibody-mediated rejection of the lung: A consensus report of the International Society for Heart and Lung Transplantation (2016)
 - i. Highlights most experts would treat a pediatric lung transplant recipient with all of the following criteria:
 - (a) Positive DSA
 - (b) C4d deposition on immunohistochemistry
 - (c) Abnormal histopathology
 - (d) Substantial graft dysfunction
 - ii. No specific guidelines on recommended treatment regimens.
- F. Measuring Overall Immunosuppression
- 1. There is no single test to evaluate the overall state of immunosuppression; however, the presence of opportunistic or recurrent infections may signify over-immunosuppression.
 - 2. It is extremely difficult to impossible to determine the minimal level of immunosuppression required for each SOT patient.
- G. Quality of Evidence in Pediatric SOT
- 1. Because of the nature of transplantation, there are currently only limited significant randomized controlled trials in SOT (both pediatric and adult patients).
 - 2. Much of the data to support current practices in SOT are based on case-controlled trials without randomization, cohort studies, case-control–analytic studies, several time series, uncontrolled experiments, or expert opinion.
 - a. This is especially true in pediatric SOT because much of the evidence is based on larger sets of data from adult SOT recipients. The limited available data in this population not only apply to immunosuppressive therapy, but also to the prevention and treatment of infectious and many noninfectious posttransplant complications.
 - b. Because of these limited available data, transplant centers may vary from one to another with respect to induction, maintenance immunosuppression, and rejection treatment strategies.

XI. CORTICOSTEROIDS

- A. CCS Are Effective at Reducing Inflammation in Diseases Such as:
- 1. Rheumatoid arthritis
 - 2. Nephrotic syndrome
 - 3. Allergic reactions
- B. CCS treatment Was Translated Over to the Transplant Population

- C. Mechanism of Action Decreases:
 - 1. Prostaglandin and cytokine synthesis
 - 2. Histamine and bradykinin release
 - 3. Capillary permeability
- D. Dosing
 - 1. Often high dose immediately pre- and posttransplantation: Intravenous methylprednisolone
 - 2. Taper posttransplantation (typically oral prednisone or prednisolone): No standard steroid taper. Steroid taper is dependent on transplant program, organ transplanted, induction agent, and other maintenance medications.
- E. Adverse Effects – Especially of Issue for the Pediatric Population:
 - 1. Glucose metabolism impairment
 - 2. Hypertension
 - 3. Growth suppression
 - 4. Osteoporosis
 - 5. Delayed wound healing
 - 6. Peptic ulcer
 - 7. Emotional fluctuation
 - 8. Acne
 - 9. Insomnia
 - 10. Cushing syndrome
 - 11. Edema

XII. CALCINEURIN INHIBITORS USED FOR SOLID ORGAN TRANSPLANTATION

- A. Cyclosporine
 - 1. Mechanism of action:
 - a. Prevents IL-2 transcription; binds to cyclophilin and then forms a complex with cyclophilin, calcium, calmodulin, and calcineurin; and prevents the dephosphorylation and translocation of nuclear factor of activated T cells.
 - b. Inhibits T-cell activation and replication.
 - 2. Formulations
 - a. Cyclosporine non-modified (Sandimmune) (Novartis)
 - i. Oral, liquid-filled capsules (25, 100 mg)
 - (a) Original oil-based formulation
 - (b) High inter- and inpatient variability
 - (c) Bile salts necessary to emulsify oil formulation for cyclosporine absorption through the gut.
 - ii. Oral solution (100 mg/mL)
 - iii. Intravenous infusion (50 mg/mL): Must be diluted before infusion.
 - b. Cyclosporine modified (Neoral) (Novartis)
 - i. Microemulsion
 - (a) Oral capsule (25, 100 mg)
 - (b) Oral solution (100 mg/mL)
 - ii. More reliable absorption versus non-modified formulation.
 - iii. Not interchangeable with cyclosporine non-modified.
 - c. Generics: Many generics exist; close TDM recommended when switching from one generic formulation to another because of the narrow therapeutic index (NTI) classification of cyclosporine.
 - i. Gengraf: Branded generic formulation of cyclosporine modified (microemulsion)

- ii. Oral capsule (25, 50, and 100 mg)
 - iii. Oral solution (100 mg/mL)
 - iv. Intravenous infusion (50 mg/mL): Must be diluted before infusion.
 - 3. Duration
 - a. Non-microemulsion half-life in adults: Around 10–27 hours (may be shorter in pediatric patients)
 - b. Microemulsion half-life in adults: Around 5–18 hours (may be shorter in pediatric patients)
 - 4. Administration/dosing
 - a. Oral
 - i. Dose range of 8–18 mg/kg/day. Typically dosed twice daily, but may require thrice-daily dosing if the patient has accelerated drug clearance.
 - ii. Trough concentration or 2 hours post-dose concentration (C₂) is used to determine maintenance dose.
 - b. Intravenous
 - i. Continuous intravenous infusion or divided doses
 - ii. Conversion of oral to intravenous is 3:1.
 - iii. Intravenous formulation contains polyethoxylated castor oil, which has been implicated in anaphylactic reactions.
 - iv. Non-polyvinyl chloride (PVC) tubing should be used to minimize leaching of di(2-ethylhexyl)phthalate (DEHP).
 - v. Intravenous route generally not preferred unless oral/enteral route is not an option
 - 5. Monitoring
 - a. NTI drug
 - b. Trough monitoring of whole blood
 - i. Poorly correlated with area under the curve (AUC).
 - ii. Target of around 150–400 ng/mL, but highly dependent on transplant center protocols, type of transplantation, and individual patient.
 - c. C₂ correlates best with AUC. Target of around 600–1500 ng/mL, but highly dependent on transplant center protocols, type of transplant, time since transplant, and individual patient.
 - d. Cannot obtain concentrations from any intravenous line that cyclosporine infused through because it binds to the catheter and may be inaccurate, even with flushing and waste.
- B. Tacrolimus (FK506)
- 1. Mechanism of action:
 - a. Prevents transcription of IL-2: Binds to FK506-binding protein (FKBP12); then forms a complex with FKBP12, calcium, calmodulin, and calcineurin and prevents the dephosphorylation and translocation of translocation of nuclear factor of activated T cells.
 - b. Inhibits T-cell activation and replication.
 - 2. Formulations
 - a. Immediate release (Brand Prograf)
 - i. Oral capsules (0.5, 1, and 5 mg)
 - ii. Intravenous infusion (5 mg/mL): Must be diluted before administration.
 - iii. 0.5- or 1-mg/mL oral suspension may be compounded: Consistency in strength is essential to avoid medication errors.
 - iv. Oral granule packets (0.2 mg and 1 mg): Mix contents in glass cup with 15–30 mL of room temperature water and give immediately. Rinse cup with water (same amount) and give orally or enterally. Avoid contact with products that contain PVC. When converting from oral immediate-release capsules, total daily dose should be equivalent.
 - v. Immediate-release generics: Many generics exist; close TDM recommended when switching from one generic formulation to another because of the NTI classification of tacrolimus.

- b. Tacrolimus XL (Brand Astagraf XL)
 - i. Extended-release, once-daily tacrolimus
 - ii. U.S. Food and Drug Administration (FDA) approved for adult and pediatric kidney transplant recipients
 - iii. Oral capsules (0.5, 1, and 5 mg)
- c. LCP-tacrolimus (Brand Envarsus XR)
 - i. Extended-release, once-daily tacrolimus with enhanced bioavailability compared with immediate-release tacrolimus.
 - ii. Not dose equivalent to immediate-release tacrolimus, though a 15%–30% daily dose reduction is generally required when transitioning from immediate-release tacrolimus to Envarsus XR.
 - iii. Safety and efficacy not established in pediatric population.
 - iv. Oral tablet (0.75 mg, 1 mg, 4 mg)
- 3. Duration
 - a. Immediate release formulations: Half-life in pediatric patients is around 8–16 hours.
 - b. Extended-release formulation: Half-life in adults is around 35–41 hours.
- 4. Administration/dosing
 - a. Oral/enteral
 - i. Tacrolimus immediate-release capsules: Typically dosed twice daily, but may require thrice-daily dosing if the patient has accelerated drug clearance.
 - ii. Compounded 0.5- or 1-mg/mL oral suspension: Typically dosed twice daily, but may require thrice-daily dosing if the patient has accelerated drug clearance. Tends to have reduced absorption compared with the immediate-release capsules.
 - iii. Tacrolimus extended-release capsules: Dosed once daily.
 - iv. Dosing strategy for all oral formulations: Often depends on induction strategy used and organ transplanted, but typically, initial dosing is 0.05–0.2 mg/kg/day.
 - v. Tacrolimus rate and extent of absorption can be decreased when administered with food (especially food with high fat content) with oral formulations; thus, consistency of administration with or without food is essential.
 - b. Intravenous
 - i. Continuous intravenous infusion.
 - ii. Conversion of oral to intravenous is 3:1–4:1.
 - iii. Intravenous formulation contains polyethoxylated castor oil, which has been implicated in anaphylactic reactions.
 - iv. Do not use PVC tubing for intravenous administration.
 - c. Sublingual
 - i. Contents of oral, non–extended-release capsules may be placed under the tongue for sublingual administration.
 - ii. Sublingual dose may result in about a 2 times higher drug concentration than an equally potent oral dose. Dose reduction when switching from oral formulation may be necessary, with close TDM.
- 5. Monitoring
 - a. NTI drug
 - b. Trough monitoring of whole blood
 - i. Correlates well with AUC.
 - ii. Target is typically 5–15 ng/mL, but specific range is highly dependent on transplant center protocols, type of transplantation, and individual patient.
 - iii. Drug serum concentrations should not be collected from the same lumen in which intravenous tacrolimus is infused.

C. Adverse Effects

1. Nephrotoxicity

a. Acute CNI nephrotoxicity

- i. Directly related to dose (and AUC).
- ii. Vasoconstriction of afferent arterioles and reduced GFR (glomerular filtration rate): Results in hyperkalemia, hypomagnesemia, hypertension, and renal dysfunction.
- iii. Cases of thrombotic microangiopathy/HUS thought to be caused by CNIs have also been documented, although this is not believed to be dose related.

b. Chronic CNI nephrotoxicity

- i. Irreversible damage may occur in all components of the kidney.
- ii. SCr is not always reflective of chronic CNI renal dysfunction, but toxicity may be noted on biopsy pathology.

2. Neurotoxicity

- a. Tremor, headache, insomnia, and paresthesia most common.
- b. Seizures, expressive aphasia, coma, delirium, and leukoencephalopathy are rare.

3. Hyperglycemia

- a. Posttransplant diabetes mellitus (PTDM)
- b. Increased risk with CCS
- c. Proposed mechanism: CNIs inhibit gene transcription, increase insulin resistance, and increase glucose intolerance.

4. Cardiovascular disease

- a. Hypertension
- b. Hyperlipidemia

5. Electrolytes

- a. Hyperkalemia
- b. Hypomagnesemia
- c. Hyperuricemia

6. GI: Nausea, diarrhea, and vomiting. Of note, in diarrhea caused by intestinal inflammation, blood concentrations of both cyclosporine and tacrolimus may significantly increase. This is because the activity of the intestinal cytochrome P450 (CYP) 3A and the efflux pump ability of P-glycoprotein to excrete tacrolimus and cyclosporine back into the intestinal lumen are decreased in the setting of intestinal inflammation.

7. Other:

- a. Alopecia with tacrolimus
- b. Hirsutism with cyclosporine

Table 3. Relative Incidence of CNI Adverse Events

Adverse Events Incidence: CsA vs. TAC	
Nephrotoxicity	CsA ~ TAC
Hypertension	CsA > TAC
PTDM	TAC > CsA
Neurotoxicity	TAC > CsA
Hyperlipidemia	CsA > TAC
Hirsutism	CsA only
Alopecia	TAC only
Gingival hyperplasia	CsA only

CsA = cyclosporine; PTDM = posttransplant diabetes mellitus; TAC = tacrolimus.

D. Drug Interactions

1. CNIs are CYP3A4 substrates (and moderate CYP3A4 inhibitors).
2. Major CYP3A4 inhibitors will increase CNI concentrations. Commonly used examples:
 - a. Azole antifungal agents
 - i. Fluconazole
 - (a) Although fluconazole is primarily excreted in the urine as unchanged drug, will see increase in CNI concentration. Empiric dose decrease likely necessary.
 - (b) Interaction sometimes used to “boost” CNI concentrations in pediatric patients.
 - (c) Dose-related CYP3A4 inhibition.
 - ii. Ketoconazole
 - (a) Interaction sometimes used to “boost” CNI concentrations.
 - (b) Of note, many transplant recipients may be receiving proton pump inhibitors, which can significantly decrease the AUC of ketoconazole.
 - iii. Itraconazole/voriconazole/posaconazole
 - (a) All of these agents will significantly increase CNI trough concentrations.
 - (b) Lower doses of CNI will be required.
 - (c) Voriconazole: Recommended to reduce tacrolimus dose by 66%, cyclosporine by 50% empirically.
 - b. Calcium channel blockers
 - i. Nifedipine, isradipine, and amlodipine may be used (minimal effects).
 - ii. Use caution with diltiazem, verapamil, and nifedipine because of potent CYP3A4 inhibition.
 - c. Macrolide antibiotics
 - i. Azithromycin may be used (minimal effects).
 - ii. Use caution with erythromycin and clarithromycin because of potent CYP3A4 inhibition.
 - d. Protease inhibitors – VERY potent inhibition
 - e. Diet – Grapefruit juice
3. Major CYP3A4 inducers will decrease CNI concentrations. Commonly used examples:
 - a. Anticonvulsants: Carbamazepine, phenobarbital, fosphenytoin, phenytoin
 - b. Antituberculosis agents: Rifabutin, rifampin
 - c. Nafcillin
 - d. Herbals: St. John’s wort
4. Nephrotoxins: Avoid additional nephrotoxins in combination with CNIs.
 - a. NSAIDs (nonsteroidal anti-inflammatory drugs): Naproxen, ibuprofen, aspirin (may be used in low doses), ketorolac, diclofenac, indomethacin, etc.
 - b. Aminoglycosides, colistin, and amphotericin B
5. Statins can have their AUC increased by CNIs.
 - a. Overlap between affinity to CYP3A4 and affinity to P-glycoprotein
 - b. Lovastatin: AUC increased by around 5- to 20-fold with cyclosporine
 - c. Simvastatin: AUC increased by around 8-fold with cyclosporine
 - d. Pitavastatin: AUC increased by around 5-fold with cyclosporine
 - e. Use: Atorvastatin, rosuvastatin, or pravastatin if a statin is required

XIII. ANTIPROLIFERATIVE AGENTS**A. Azathioprine**

1. Mechanism of action: Guanosine analog that antagonizes the metabolism of purines and inhibits DNA/RNA synthesis

2. Metabolism: Converted in liver to active agent, mercaptopurine → metabolized by xanthine oxidase, thiopurine methyltransferase (TPMT), and hypoxanthine guanine phosphoribosyltransferase (forms 6-thioguanine nucleotides)
 - a. Azathioprine cytotoxicity occurs because of the incorporation of 6-thioguanine nucleotides into DNA.
 - b. Patients with intermediate, low, or absent TPMT activity are at an increased risk of bone marrow suppression.
3. Formulations
 - a. Brand Imuran: Oral tablet (50 mg)
 - b. Generic: Oral tablet (50 mg)
 - c. Compounded oral suspension 10 mg/mL or 50 mg/mL
4. Dosing: Initial dose typically 1–2 mg/kg once daily for pediatric patients with SOT.
5. Adverse effects:
 - a. Most common adverse effects: Leukopenia, anemia, and thrombocytopenia
 - b. Less common adverse effects: Alopecia, pancreatitis, and hepatotoxicity
6. Drug interactions: Allopurinol inhibits xanthine oxidase.
 - a. Significant increase in mercaptopurine exposure.
 - b. Recommended to decrease azathioprine by 75% if no other alternatives.
7. Replaced by mycophenolate mofetil/mycophenolate sodium in many transplant centers.

Patient Case

1. J.N. is a 4-year-old Hispanic female patient with a history of megacystic microcolon intestinal hypoperistalsis after a multivisceral transplant (liver, kidney, spleen, and intestine) more than 3 years ago. She is seen in the pediatric GI clinic today for a routine clinic follow-up. It is noted on her laboratory test results that her SCr increased from 0.25 mg/dL at her last visit 1 month ago to 1.41 mg/dL today. Her tacrolimus trough concentration increased from 6.3 ng/mL 1 month ago to 18.2 ng/mL today. She is given a diagnosis of an acute kidney injury, believed to have been caused by the large increase in tacrolimus exposure. J.N.'s mother explains several recent changes in J.N.'s routine and care. Which most likely led to the large increase in J.N.'s tacrolimus trough concentration?
 - A. She switched from compounded suspension made with brand tacrolimus (Prograf) to compounded suspension made with generic tacrolimus (Sandoz) 2 weeks ago.
 - B. Under the direction of the pediatric transplant dietitian, her enteral feeds were increased by 20% 1 month ago.
 - C. She has had significantly increased stool output for the past 5 days.
 - D. Her mother accidentally gave an extra dose of tacrolimus 2 weeks ago because of the formulation change.

B. Mycophenolate (Mycophenolic Acid)

1. Mechanism of action: Noncompetitive inhibitor of inosine monophosphate dehydrogenase
 - a. Mycophenolic acid (active metabolite) inhibits the de novo synthesis pathway of guanosine nucleotides without being incorporated into DNA.
 - b. T and B lymphocytes dependent on de novo synthesis pathway for proliferation; neither has salvage pathways for guanosine synthesis like other cell types.
2. Formulations
 - a. Mycophenolate mofetil (CellCept)
 - i. 250-mg capsules, 500-mg tablets – Many generic formulations available.
 - ii. Commercially available as a 200-mg/mL suspension.
 - iii. 500-mg/vial injection: Must be diluted before administration.

- iv. Inactive 2, 4-morpholinoethyl prodrug ester of mycophenolic acid: Cleaved to mycophenolic acid before absorption in small intestine.
- b. Mycophenolate sodium (Myfortic) – 180- and 360-mg tablets – Generic formulation(s) available
 - i. Sodium salt of mycophenolate
 - ii. Because mycophenolate sodium is available only as a delayed-release tablet and is unavailable in a liquid preparation, this option has limited utility in the younger pediatric population.
3. Mycophenolate mofetil versus mycophenolate sodium

Table 4. Comparison of MMF and MPS

	MMF (CellCept)	MPS (Myfortic)
Pediatric dosing	1200 mg/m ² /day divided twice daily (maximum dose of 1000 mg twice daily) with CsA 900 mg/m ² /day divided twice daily (maximum dose of 1000 mg twice daily) with TAC or no CNI has been recommended or 20–50 mg/kg/day divided twice daily	BSA < 1.19 m ² : MPS not recommended BSA 1.19–1.58 m ² : 540 mg by mouth twice daily BSA > 1.58 m ² : 720 mg by mouth twice daily
Conversion to MPA^a	0.739:1	1:1
Generic availability	Yes	Yes
Administration	Enteral, IV, oral (capsules, tablets, suspension)	Oral (delayed-release tablets)
Monitoring	IV – Administer over at least 2 hours Oral – Do not crush, chew, or cut; avoid inhalation	Oral – Do not crush, chew, or cut tablets

^a(1 g MMF) x 0.739 = 739 mg of MPA vs. 720 mg of mycophenolate Na⁺ = 720 mg MPA.

BSA = body surface area; IV = intravenous; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MPS = mycophenolate sodium

4. Concurrent medications
 - a. Rifampin and cyclosporine: Decrease mycophenolic acid AUC.
 - b. Antibiotics: Decrease mycophenolic acid exposure through interference of normal gut flora.
 - c. Cholestyramine, probenecid, antacids: Bind mycophenolic acid → decrease mycophenolic acid exposure by up to 40%.
 - d. Cyclosporine: Decrease mycophenolic acid exposure by up to 40%.
5. Adverse effects: Diarrhea, anemia, leukopenia, and vomiting
6. Monitoring
 - a. Mycophenolic acid trough concentrations and/or abbreviated AUCs are performed at select transplant centers.
 - b. Utility of drug concentrations is not well defined in the pediatric transplant literature.
7. Pregnancy
 - a. Pregnancy risk category D: Mycophenolic acid or mycophenolate associated with first-trimester pregnancy loss and congenital malformations, including, but not limited to, external ear malformation, cleft lip/palate, and anomalies of the kidneys.

- b. Risk Evaluation and Mitigation Strategies (REMS) components
 - i. Medication guide
 - ii. Elements to ensure safe use
 - (a) Health care provider education
 - (b) Centralized pregnancy registry: Recommended that female exposures to mycophenolic acid or mycophenolate during pregnancy be reported to the Mycophenolate Pregnancy Registry (<https://www.mycophenolaterems.com/#Main/ReportAPregnancy>).
- c. For females with reproductive potential who are sexually active on mycophenolic acid or mycophenolate, one of the following strategies is recommended:
 - i. Intrauterine device, tubal sterilization, or vasectomy of the female patient's partner may be used alone.
 - ii. Hormonal contraception plus one barrier method
 - iii. Two barrier methods
- d. Pregnancy testing recommended immediately before therapy, 8–10 days after therapy initiation, and at routine clinic follow-up visits as necessary or indicated.

XIV. MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

- A. Mechanism of Action
 - 1. Binds to FKBP12, forming a complex that prevents stimulation of mTOR by IL-2.
 - 2. Inhibits cell cycle by preventing signaling that triggers cell progression from G1 to S phase.
 - 3. Inhibits T-cell proliferation and differentiation.
- B. Formulations
 - 1. Sirolimus (Rapamune): Available as a 1-mg/mL solution and 0.5-, 1-, and 2-mg tablets; generic formulation approved in the United States. Sirolimus solution must be refrigerated and protected from light.
 - 2. Everolimus (Zortress): Available as 0.25-, 0.5-, 0.75-, and 1-mg tablets; generic formulation approved in the United States. Brand Afinitor tablets and soluble tablets (Afinitor Disperz) not approved for SOT.
- C. Metabolism and Duration
 - 1. Everolimus and sirolimus metabolized in the gut and liver by CYP3A4 and P-glycoprotein.
 - 2. Sirolimus: Pediatric half-life of around 60 hours
 - 3. Everolimus: Pediatric half-life of around 35 hours
- D. Dosing/Administration
 - 1. Sirolimus
 - a. Loading dose of 3 mg/m² on day 1 (maximum initial loading dose typically 6 mg) and then a maintenance dose of 1 mg/m² once daily thereafter (maximum initial maintenance dose typically 2 mg). Because of a shorter half-life in younger patients compared with adults, some pediatric patients may require twice-daily dosing.
 - b. Trough concentration targets (about 24 hours from previous dose with daily dosing and about 12 hours from previous dose if twice-daily dosing)
 - i. In combination with CNI and a CCS: Typically 5–12 ng/mL
 - ii. In CNI-free regimen: Typically 12–24 ng/mL in the first year after transplantation
 - c. Solution: Mix dose in a cup with at least 60 mL of water or orange juice and drink immediately. Refill cup with another 120 mL of water or orange juice, mix, and drink immediately. This administration volume may be challenging for younger pediatric patients.

2. Everolimus
 - a. Data for pediatric transplantation are limited, although 0.8 mg/m² twice daily has been suggested.
 - b. Trough concentration targets for adult transplant patients (about 12 hours from previous dose)
 - i. In combination with CNIs and a CCS: Typically 3–8 ng/mL
 - ii. In a CNI-free regimen: Typically 6–10 ng/mL
- E. Most Common Adverse Effects: Leukopenia, anemia, thrombocytopenia, delayed wound healing, oral ulcers, hyperlipidemia, and proteinuria
 1. Because of the significant wound healing issues, mTOR inhibitors are typically not initiated immediately posttransplantation and may need to be converted to another agent for a major elective surgery.
 2. Sirolimus has also been associated with hepatic artery thrombosis when initiated at transplantation in liver transplant recipients.
- F. Drug Interactions
 1. Metabolized by CYP3A4 substrate: See CNI section (III) for examples of interactions with CYP3A4 inducers and inhibitors.
 2. Both sirolimus and cyclosporine concentrations increase when both are used in combination (administration must be separated), but this interaction is different when sirolimus and tacrolimus are used in combination.

XV. LYMPHOCYTE-DEPLETING AGENTS

- A. Rabbit Antithymocyte Globulin
 1. Polyclonal antibody
 2. Produced by immunizing rabbits against human lymphocytes, followed by extracting the antilymphocyte antibodies to make rATG.
 3. Mechanism
 - a. Binds T-cell surface antigens (CD3, CD4, CD8, CD11a, CD18, CD25, CD28, CD2, CD5, CD44, CD45, CD154), B-cell surface antigens (CD20), and NK cell antigens (CD16, CD56).
 - b. Depletes circulating T lymphocytes and alters/modulates the action of T lymphocytes.
 4. Duration: Although the half-life is about 2–3 days, the biologic effects last for up to 9–12 months.
 5. Use
 - a. Induction: Many centers will use rATG for induction as part of a rapid steroid withdrawal protocol or if the recipient has a PRA of 30%–50% or greater.
 - b. Treatment of moderate to severe, recurrent, or steroid-resistant acute cellular rejection
 6. Dosing/administration
 - a. Intraoperative administration (starting before the anastomosis of the transplanted organ) preferred to postoperative administration because of decreased rates of ischemia-reperfusion injury and decreased rates of delayed graft function.
 - b. Dosing dependent on organ type and transplant center-specific guidelines. For induction, typically 1–1.5 mg/kg intravenously daily for 4–7 days, but may require longer if used to treat acute cellular rejection. May consider monitoring CD3 count to assess need for additional doses.
 - c. Dosing recommendations for kidney transplant recipients:
 - i. Decrease dose by 50% when the WBC is $2\text{--}3 \times 10^3$ cells/mm³.
 - ii. Hold if WBC is less than 2×10^3 cells/mm³.
 - iii. Decrease dose by 50% when platelet count is 50,000–70,000/mm³.
 - iv. Hold if platelet count is less than 50,000/mm³.
 - d. Administer through a 0.22-micron filter.

- e. Infuse over 4–12 hours: First dose over 6 hours and then subsequent doses over 4–6 hours, although dependent on tolerability of doses and intravenous access (central vs. peripheral line).
 - f. Central versus peripheral intravenous administration
 - i. Central intravenous access preferred with a maximum concentration of 0.5 mg/mL.
 - ii. Peripheral intravenous not optimal, but may be used if central access cannot be obtained.
 - iii. Because of concerns with increased incidence of phlebitis, heparin and hydrocortisone are added to the intravenous rATG preparation for pediatric patients at select transplant centers.
 - g. To prevent severe infusion-related reactions, premedicate 30–60 minutes prior with:
 - i. CCS (e.g., intravenous methylprednisolone); if CCS are already part of the patient's immunosuppressive regimen, consider timing before rATG.
 - ii. Acetaminophen
 - iii. Diphenhydramine
 - h. Consider adding emergency medications (diphenhydramine, hydrocortisone, epinephrine) because of increased risk of reaction.
7. Adverse effects
- a. Lymphopenia for up to 1 year after rATG treatment
 - b. Cytokine release syndrome: Flu-like symptoms, fever, chills, dyspnea, nausea/diarrhea, headache, pain, pulmonary edema
 - c. Leukopenia, thrombocytopenia
 - d. Increased risk of infection
 - e. Increased risk of malignancy
 - f. Rare: Allergy, antibody formation against horse or rabbit antigen, serum sickness (often presents as a delayed reaction)
- B. Equine Antithymocyte Globulin Not Commonly Used in Pediatric SOT Because:
- 1. rATG is associated with lower acute rejection rates than eATG.
 - 2. rATG is superior to eATG at treating acute rejection episodes in renal transplant recipients.
- C. Alemtuzumab (Campath)
- 1. Humanized anti-CD52 monoclonal antibody
 - 2. Mechanism of action
 - a. CD52 is a binding protein found on activated T cells.
 - b. Activated T cells release IL-2 that binds to and activates CD52, which is also found on B cells, macrophages/monocytes, NK cells, and some granulocytes, leading to stimulation of the cycle causing T-cell replication. CD52 also found on B cells, macrophages/monocytes, NK cells, and some granulocytes. Alemtuzumab eliminates T cells by binding to CD52, ultimately causing cell lysis.
 - 3. Duration: Although its half-life ranges from 11 hours to 6 days, the biologic effects last up to several years.
 - 4. Use: Used off-label as an induction agent and, in certain cases, has been used to treat moderate to severe rejection (rare).
 - 5. Dosing/administration
 - a. Administered intravenously (central or peripheral line) over 2 hours or subcutaneously.
 - b. Premedicated with CCS, diphenhydramine, and/or acetaminophen.
 - c. Adult dosing for induction is 30 mg at transplantation.
 - d. Pediatric dosing for induction is around 0.5 mg/kg at transplantation (maximum dose of 30 mg) (limited data).
 - 6. Adverse effects
 - a. Flu-like symptoms, fever, chills, nausea, diarrhea, vomiting, headache, dizziness
 - b. Neutropenia, anemia, thrombocytopenia
 - c. Increased risk of infection
 - d. Increased risk of malignancy

7. Of note, alemtuzumab (Campath) was withdrawn from the U.S. market in 2012. In November 2014, it was FDA approved for the treatment of relapsing forms of multiple sclerosis at doses of 12 mg intravenously but marketed under the brand name Lemtrada. As of July 2020, alemtuzumab (Campath) remains available through the Campath Distribution Program for B-cell chronic lymphocytic leukemia and several unlabeled indications, including induction for SOT and steroid resistant rejection.

D. Rituximab (Rituxan)

1. Chimeric monoclonal antibody
2. Mechanism of action: Rituximab reacts with CD20 antigen, inhibiting B-cell proliferation. CD20 transmembrane protein located on pre-B and mature B cells, but not on plasma cells
3. Duration: 6–12 months
4. Use
 - a. Treatment of AMR
 - b. Desensitization: Decrease concentrations of preformed antibodies to cause a positive crossmatch (typically for a living donor) to become negative, typically as part of a multidrug regimen
 - c. Induction (in rare cases, such as a crossmatch positive transplant where AMR is anticipated, as part of a multidrug regimen)
 - d. Treatment of posttransplant lymphoproliferative disorder
5. Dosing/administration
 - a. 375 mg/m² intravenous infusion: Total number of weekly doses varies in the literature, depending on the indication.
 - b. Premedication with diphenhydramine and acetaminophen recommended (30–60 minutes prior to infusion) with emergency doses of epinephrine, diphenhydramine, and CCS.
6. Adverse effects
 - a. Pancytopenia
 - b. Infusion reactions such as flu-like symptoms, fever, chills, headache, and myalgias, including anaphylaxis
 - c. Infection (herpes zoster)

XVI. INTERLEUKIN-2 RECEPTOR ANTAGONISTS

A. Basiliximab (Simulect)

1. Chimeric monoclonal antibody
2. Mechanism of action
 - a. Binds to the IL-2 receptor (CD25) with high affinity.
 - b. The antagonistic effect on CD25 prevents T-cell activation and proliferation.
 - c. Does not cause lymphocyte depletion.
3. Duration: Basiliximab occupies CD25 for 5–8 weeks.
4. Use
 - a. Induction for SOT
 - b. Not used to treat acute rejection.
5. Dosing/administration
 - a. Pediatric dosing
 - i. Less than 35 kg: 10 mg within 2 hours of transplantation and on postoperative day 4
 - ii. 35 kg or greater: 20 mg within 2 hours of transplantation and on postoperative day 4
 - b. Intravenous infusion over 20–30 minutes
 - c. Premedication not necessary.

6. Adverse effects: No increased adverse effects compared with placebo, and hypersensitivity reactions are rare.

XVII. OTHER BIOLOGIC AND NOVEL AGENTS IN SOLID ORGAN TRANSPLANTATION

A. Belatacept (Nulojix)

1. Human fusion protein combining extracellular portion of CTLA-4 with constant-region fragment (Fc) of human IgG1
2. Mechanism of action: Binds surface co-stimulatory ligands (CD80 and CD86) of antigen-presenting cells to block co-stimulation and T-cell activation. The interaction of CD80 and CD86 with surface co-stimulatory receptor CD28 of T cells (signal 2) is required for T-cell activation.
3. Duration: Half-life of about 10 days
4. Use
 - a. Approved for maintenance therapy in kidney transplant recipients 18 years and older in combination with mycophenolate mofetil and CCS with basiliximab induction. Used in place of CNIs.
 - b. Not currently approved for pediatric patients because of concern for posttransplant lymphoproliferative disorder (PTLD). Ongoing studies are cautiously reviewing use in the pediatric population and determining optimal pediatric dosing/pharmacokinetics.
 - c. Contraindicated in patients who are Epstein-Barr virus (EBV) seronegative or if EBV status is unknown.
5. Dosing/administration
 - a. Adult dosing: 10 mg/kg intravenously before implantation; 10 mg/kg on postoperative day 4; 10 mg/kg at the end of weeks 2, 4, 8, and 12 after transplantation; then 5 mg/kg every 4 weeks
 - b. Administration: Intravenous infusion over 30 minutes with a 0.2- to 1.2-micron filter
6. Adverse effects
 - a. Infusion reactions
 - b. PTLD
 - c. Infection (including tuberculosis)
7. Belatacept Evaluation of Nephroprotection and Efficacy as First-line Immunosuppression Trial (BENEFIT)
 - a. Showed that belatacept, in adult renal transplant recipients, allows for effective immunosuppression with better preservation of renal function, possible improved cardiovascular/metabolic risks, and less toxicity compared with cyclosporine.
 - b. Of note, patients receiving belatacept had a higher incidence of PTLD and acute rejection.
8. REMS program/registry
 - a. When first approved, the FDA mandated a REMS program for belatacept, including a medication guide and communication guide. As of May 2017, the FDA determined that a REMS program is no longer mandatory for belatacept. Patients are required to be enrolled in the Nulojix Distribution Program to access the drug.

B. Bortezomib (Velcade)

1. Dipeptidyl boronic acid proteasome inhibitor
2. Currently approved for the treatment of multiple myeloma and mantle cell lymphoma.
3. Mechanism of action
 - a. Inhibits 26S proteasome, which disrupts cell homeostasis and death.
 - b. Inhibits activation of nuclear factor- κ B through stabilization of inhibitor protein I κ B.

- c. Immune-modulating effects are pleiotropic and has anti-myeloma properties, partly because of potent proapoptotic effects.
 - i. In addition to anti-plasma cell properties, may suppress T-cell function; therefore, treat cellular rejection as well.
 - ii. Inhibition of IL-6 by bone marrow cells leads to apoptosis at various stages in B-cell maturation.
 - 4. May have utility for transplantation in the management of highly sensitized patients and/or treatment of humoral rejection, although data, especially in pediatric patients, are very limited.
 - a. The limitation of many current anti-humoral therapies (e.g., plasmapheresis, plasma exchange, rituximab) is lack of effect on the major antibody-producing cell (the mature plasma cell).
 - b. Bortezomib use typically reserved for treatment of AMR when other strategies have failed to successfully decrease antibody titers.
 - i. Typically, plasmapheresis with IVIG and rituximab used prior.
 - ii. Bortezomib 1.3 mg/m²/dose intravenously or subcutaneously every 72 hours x 4 or 5 doses has been used.
 - iii. Adverse effects include GI toxicity, myelosuppression, and peripheral neuropathy.
- C. Eculizumab (Soliris)
- 1. Humanized monoclonal antibody
 - 2. Mechanism of action: Binds complement protein C5, preventing the cleavage into C5a and C5b by C5 convertase; prevents formation of the membrane attack complex (terminal complex C5b-9).
 - 3. Duration: Half-life of about 8–15 days
 - 4. Use
 - a. Approved for aHUS and paroxysmal nocturnal hemoglobinuria.
 - b. Also has been reported in SOT for treatment of AMR and as part of desensitization protocols.
 - 5. Dosing/administration
 - a. Dosing and frequency vary depending on transplant center for off-label uses, including treatment of an AMR, and is often extrapolated from aHUS data.
 - b. Dosing for aHUS (see Nephrology chapter)
 - c. Supplemental doses of eculizumab are required after plasmapheresis or plasma exchange. Supplemental doses are required before fresh frozen plasma infusions.
 - d. It is unlikely that eculizumab is removed with hemodialysis or peritoneal dialysis because of the molecular size of eculizumab; thus, supplemental doses are not routinely recommended after hemodialysis or peritoneal dialysis.
 - e. Patients should receive the quadrivalent meningococcal conjugate vaccine at least 2 weeks before treatment with eculizumab. Patients are at increased risk of infections, especially by encapsulated bacteria. Patients 10 years and older should also receive the serogroup B meningococcal vaccine.
 - f. Prophylaxis with an antibiotic that provides coverage against encapsulated bacteria (e.g., *Neisseria meningitidis*) may be used for patients who are receiving vaccine and eculizumab at the same time for at least 2 weeks up to lifetime.
 - 6. REMS program: Eculizumab is available only through restricted distribution, which requires providers to enroll in a REMS program. Providers are required to educate patients about the risk of meningococcal infections, provide REMS educational materials to patients, and ensure that patients are appropriately vaccinated with the meningococcal vaccine.
 - 7. Ravulizumab-cwvz (Ultomiris), a C5 inhibitor that differs from eculizumab by 4 amino acids, is also approved for aHUS in pediatric patients.
 - a. The half-life of ravulizumab-cwvz is around 4-fold that of eculizumab.

Patient Cases

2. K.G., a 13-year-old African American female patient with ESRD secondary to IgA nephropathy was admitted from home for a deceased donor kidney transplant today. The kidney donor and recipient are mismatched for six of six HLA antigens (two HLA-A mismatches, two HLA-B mismatches, and two HLA-DR mismatches). The time from when the transplanted kidney was not perfused on removal from the donor to the time of organ implantation (cold ischemic time) was 12 hours. The recipient has a calculated PRA of 80%. The donor was CMV IgG positive, and the recipient was CMV IgG positive, previously. The donor is EBV IgG positive, and the recipient was previously EBV IgG positive. No other donor and recipient serologies are significant. The donor and recipient are ABO compatible, and the transplant crossmatch was negative. The maintenance immunosuppressive plan for K.G. is tacrolimus, mycophenolate sodium, and prednisone. According to the 2009 KDIGO guidelines, which strategy would be best for transplant induction therapy?
 - A. Rituximab
 - B. rATG
 - C. No induction
 - D. Basiliximab
3. R.H. is a 7-year-old male patient with a medical history significant for a small left solitary kidney at birth after a renal transplant about 2 years ago. The patient also has a history of vesicoureteral reflux and hypertension related to transplantation. The patient presented several days ago for a renal biopsy as workup for rejection, given a recent increase in SCr. Today, the final biopsy report is suggestive of acute AMR (positive C4d staining and many lymphocytes in the peritubular capillaries). There was no evidence of acute cellular rejection on biopsy. In addition, Luminex assay results reveal strong DSA to DR53 (mean fluorescence intensity is 14,000). R.H. has not been treated for rejection in the past. His maintenance medications include amlodipine 5 mg by mouth daily; sulfamethoxazole/trimethoprim 400/80 mg by mouth daily; prednisolone 6 mg by mouth every Monday, Wednesday, Friday, and Saturday; and tacrolimus 3 mg by mouth twice daily. Which would be the best regimen to treat R.H.'s acute AMR rejection episode?
 - A. Basiliximab
 - B. Intravenous methylprednisolone
 - C. Eculizumab
 - D. Plasmapheresis plus IVIG

XVIII. ANTI-INFECTION

- A. Net State of Immunosuppression
 1. Decrease natural response to infection.
 2. Decrease inflammatory markers such as fever, WBC; delay time to discovery of infection.
 3. Increase severity and duration of infections and morbidity associated with infections.
- B. Infections and Selected Treatment
 1. Latent viruses from donor organ or recipient
 - a. Cytomegalovirus
 - i. CMV may be detected with screening of the blood/tissue using PCR or antigen testing (CMV pp 65 antigen).
 - ii. Often associated with "flu-like" symptoms.
 - iii. Can cause pneumonitis, colitis, retinitis, nephritis, carditis, and hepatitis.

- iv. Treatment (Clin Transplant 2019;33:e13512)
 - (a) Severe disease, high viral load, poor GI absorption: Intravenous ganciclovir
 - (b) Initial treatment for mild to moderate CMV disease
 - (1) Intravenous ganciclovir, or
 - (2) Oral valganciclovir (not FDA approved for treatment in children)
 - (c) Treat for at least 2 weeks. May use serial quantitative viral load to determine therapy duration.
- b. Epstein-Barr virus
 - i. EBV may be detected with screening of the blood/plasma using PCR.
 - ii. Can lead to PTLD.
 - (a) In a non-immunosuppressed individual, T cells (and NK cells) typically control EBV-infected B cells and prevent over-proliferation.
 - (b) In a significantly immunosuppressed patient, T cells can no longer control B cells, which leads to over-proliferation of B cells.
 - iii. Preemptive strategies for PTLD (Clin Transplant 2019;33:e13652)
 - (a) Reduction in immunosuppression is recommended for first-line preemptive management if the patient has a rapidly increasing EBV viral load.
 - (b) Currently, the efficacy of antiviral therapy (acyclovir, ganciclovir, and valganciclovir) with or without IVIG or rituximab or adoptive immunotherapy has not been validated. Of note, ganciclovir is 10 times more active against EBV than is acyclovir in vitro.
- c. Other herpes viruses (herpes simplex virus, human herpesvirus 8)
- d. BK virus
 - i. Can cause tubulointerstitial nephritis
 - ii. BK virus may be detected with screening of urine and blood using PCR.
 - iii. Treatment of BK polyomavirus-associated nephropathy (PyVAN) (Clin Transplant 2019;33:e13528)
 - (a) First-line treatment: Reduce immunosuppression.
 - (1) Tacrolimus goal trough concentrations less than 6 ng/mL
 - (2) Cyclosporine goal trough concentrations less than 150 ng/mL
 - (3) Sirolimus goal trough concentrations less than 6 ng/mL
 - (4) Mycophenolate mofetil/mycophenolate sodium goal daily dose of 50% or less of target daily maintenance dose
 - (b) Additional treatment strategies (poor level of evidence)
 - (1) Switching from tacrolimus to low-dose cyclosporine
 - (2) Switching from a CNI to sirolimus
 - (3) Switching from mycophenolate mofetil/mycophenolate sodium to sirolimus or leflunomide
 - (c) Additive treatment strategies for patients with persistently elevated plasma BK virus load may be considered (poor level of evidence).
 - (1) Intravenous cidofovir
 - (A) Associated with nephrotoxicity.
 - (B) Brincidofovir (CMX001), an oral lipid conjugate of cidofovir, currently under investigation for CMV, though not currently commercially available in the United States.
 - (2) Leflunomide
 - (3) IVIG
 - (4) Fluoroquinolones
- 2. Nosocomial organisms: Related to factors from the transplant surgical procedure itself and postoperative aspects of care (e.g., catheters, endotracheal tubes).

3. Opportunistic infections
 - a. *Pneumocystis jiroveci*
 - b. *Aspergillus* spp.
 - c. *Listeria monocytogenes*
 - d. *Cryptococcus* spp.
 - e. *Nocardia* spp.
 - f. Coccidioidomycosis, histoplasmosis, blastomycosis
 - g. *Candida* spp.
4. Community-acquired organisms

Patient Case

4. C.M. is a 14-year-old Hispanic male patient who presents after a deceased donor kidney transplant 3 years ago for chronic reflux nephropathy leading to renal failure. C.M. has had a fairly uncomplicated posttransplant course with no episodes of rejection. His current medication regimen is tacrolimus 2 mg by mouth twice daily, mycophenolate mofetil 500 mg by mouth twice daily, prednisone 5 mg by mouth once daily, sodium bicarbonate 650 mg by mouth three times daily, and human recombinant growth hormone subcutaneously daily. His recent chemistries have been within normal limits. Of note, his plasma EBV polymerase chain reaction (PCR) viral load results have been significantly increasing:

- 8 months ago: Not detected
- 2 months ago: Less than 300 copies/mL
- 1 month ago: 1020 copies/mL
- 1 week ago: 10,880 copies/mL

Total body computerized tomography did not reveal any significant findings because no suspicious lesions were found. According to the American Society of Transplantation infectious disease guidelines, which would be the best strategy for preemptive management of posttransplant lymphoproliferative disorder (PTLD) for C.M.?

- A. Reduction in immunosuppression
- B. Intravenous ganciclovir
- C. Intravenous ganciclovir and arginine butyrate
- D. Rituximab

C. Prophylactic Agents

1. Prophylactic agents are used to prevent infection.
 - a. Primary prophylaxis: Preventing initial infection.
 - b. Secondary prophylaxis: Preventing recurrence or reactivation of infection.
 - c. Eradication: Covering organisms for which the patient is colonized.
2. Infection prophylactic strategies vary between transplant centers and depend on organ(s) transplanted, immunosuppression used, and other environmental factors.
3. Perioperative antimicrobials
 - a. Dependent on organ(s) transplanted.
 - i. Antimicrobial agent (recommendations based on 2013 American Society of Health-System Pharmacists clinical practice guidelines for antimicrobial prophylaxis in surgery)
 - (a) Liver transplantation: Piperacillin/tazobactam or cefotaxime plus ampicillin recommended.
 - (b) Kidney transplantation: Cefazolin recommended.

- (c) Intestine and multivisceral transplantation: Typically a broad-spectrum antibiotic (e.g., piperacillin/tazobactam)
 - (d) Heart and lung transplantation: Cefazolin with or without vancomycin is recommended, although many center-specific lung transplant surgical prophylaxis guidelines include other antibiotics to eradicate organisms to which the patient is colonized/infected.
 - ii. Duration
 - (a) Typically about 24–72 hours
 - (b) Lung and heart transplant recipients: May have prophylaxis continued until mediastinal drains removed; however, there are no data to support this practice.
 - (c) Patients undergoing lung transplantation for cystic fibrosis will typically receive antimicrobial therapy for 7–14 days, depending on culture and susceptibility results.
 - b. May depend on recipient and donor factors.
 - i. Patient allergies
 - ii. Previous culture results
 - iii. In lung transplantation, donor and recipient bronchoalveolar lavage cultures often are available posttransplantation to tailor antimicrobial therapy.
- 4. Anti-*P. jiroveci* agents
 - a. Sulfamethoxazole/trimethoprim (Bactrim, Septra)
 - i. Agent of choice if the patient does not have a contraindication to it (e.g., sulfa allergy).
 - ii. Dose for prophylaxis: Varies; 5 mg of trimethoprim/kg/dose (maximum dose 160 mg trimethoprim) by mouth once every Monday, Wednesday, and Friday has been used.
 - iii. Available as tablet, suspension, and intravenous infusion.
 - iv. Duration
 - (a) Typically 6–12 months after transplant
 - (b) For lung transplantation or intestine/multivisceral transplantation, lifelong prophylaxis may be used.
 - (c) May be initiated if a patient receives a lymphocyte-depleting agent to treat acute rejection.
 - v. Adverse reactions
 - (a) Crystalluria
 - (b) Sun sensitivity
 - (c) Hyperkalemia
 - (d) Leukopenia, anemia, thrombocytopenia
 - vi. Also offers urinary tract infection prophylaxis and *Toxoplasma gondii* prophylaxis.
 - b. Aerosolized pentamidine (NebuPent)
 - i. Dose for prophylaxis is typically 300 mg inhalation monthly.
 - ii. Duration: Typically 6–12 months
 - iii. Adverse reactions: Often causes bronchospasm. Premedicate with albuterol; not the preferred alternative agent for lung transplant recipients.
 - c. Atovaquone (Mepron)
 - i. Dose for prophylaxis
 - (a) For children 1–3 months of age: 30 mg/kg by mouth once daily with food
 - (b) 4–24 months: 45 mg/kg by mouth once daily with food
 - (c) Older than 24 months: 30 mg/kg (maximum dose of 1500 mg) by mouth once daily with food
 - ii. Available only as a 750-mg/5-mL oral suspension.
 - iii. Also provides prophylaxis for *T. gondii*.
 - d. Dapsone
 - i. Dose for prophylaxis
 - (a) 2 mg/kg/day by mouth once daily (maximum dose of 100 mg)
 - (b) 4 mg/kg/dose by mouth once weekly (maximum dose of 200 mg)

- ii. Available as a tablet or extemporaneously prepared suspension.
- iii. Adverse reactions
 - (a) More than 10% of patients will experience some degree of hemolysis: More severe in patients with glucose-6-phosphate dehydrogenase deficiency.
 - (b) Skin irritation
 - (c) Hepatitis
 - (d) Methemoglobinemia
- 5. Antiviral agents
 - a. Ganciclovir (Cytovene)
 - i. Offers activity against herpes viruses, including herpes simplex virus; varicella-zoster virus; EBV; and, primarily, CMV.
 - ii. Dose for prophylaxis
 - (a) 5 mg/kg/dose intravenously every 24 hours
 - (b) Requires dose adjustment for renal impairment and dialysis (about 50% of drug removed by dialysis).
 - iii. Dosage form
 - (a) Only available as intravenous preparation.
 - (b) Oral formulation has been discontinued (see valganciclovir for oral therapy).
 - iv. Adverse reactions
 - (a) Myelosuppression
 - (b) Nephrotoxicity
 - v. Typically continued until patient is transitioned to oral valganciclovir.
 - b. Valganciclovir (Valcyte)
 - i. Oral prodrug of ganciclovir
 - ii. Offers activity against herpes viruses, including herpes simplex virus; varicella-zoster virus; EBV; and, primarily, CMV.
 - iii. Dose for prophylaxis
 - (a) Recommended adult dose: 900 mg by mouth daily (adjusted for renal function)
 - (b) Manufacturer-recommended pediatric valganciclovir dose: $7 \times (\text{body surface area}) \times (\text{creatinine clearance [CrCl] from modified Schwartz formula})$ by mouth once daily (maximum dose of 900 mg daily)
 - (1) Schwartz formula (modified): $\text{CrCl} = k \times (\text{height in cm}) / (\text{SCR in mg/dL})$; maximum $\text{CrCl} = 150 \text{ mL/minute}/1.73\text{m}^2$
 - (2) May overestimate desired ganciclovir exposure, especially in patients 6–36 months of age.
 - (3) If patients are older than 16 years, see adult dosing.
 - (c) Alternative adult and pediatric dosing strategies have been used at individual transplant centers.
 - iv. Dosage form
 - (a) Oral 450-mg tablets
 - (b) Oral 50-mg/mL commercially available solution (requires refrigeration)
 - v. Adverse reactions
 - (a) Myelosuppression (neutropenia)
 - (b) Nephrotoxicity
 - vi. Duration is typically 3–12 months, depending on donor and recipient CMV serology status.
 - vii. Valganciclovir may be reinitiated for 3–6 months if a patient receives a lymphocyte-depleting agent to treat acute rejection.

- c. Maribavir
 - i. Blocks CMV replication through competitive inhibition of human CMV enzyme pUL97.
 - ii. Dose for **treatment**
 - (a) 400 mg by mouth twice daily for patients 12 years (and ≥ 35 kg) and older
 - iii. Dosage form
 - (a) 200 mg tablet
 - iv. Adverse reactions
 - (a) Dysgeusia most common (~40%)
 - (b) Nausea, vomiting, diarrhea, and fatigue also common adverse reactions
 - v. Duration: Treatment with maribavir for 8 weeks in SOLSTICE trial
 - vi. Approved in November 2021 for **treatment** of CMV disease/infection that does not respond to first line treatment for CMV disease/infection (with or without genetic mutations)
 - (a) Has yet to be included in major CMV SOT guidelines
 - d. Acyclovir: Rarely used as antiviral prophylaxis for pediatric SOT patients because it does not provide adequate prophylaxis from CMV, although it may be used for CMV IgG-negative recipients who receive an organ(s) from a CMV IgG-negative donor.
 - e. CMV IVIG (Cytogam): Some centers will use CMV IVIG in combination with ganciclovir/valganciclovir for high-risk SOT, including lung transplantation and intestine/multivisceral transplantation, although data supporting this practice are limited.
 - f. Letermovir: An inhibitor of the CMV DNA terminase complex; approved for allogeneic hematopoietic stem cell transplantation for CMV prophylaxis with increasing, but still limited, data in the adult SOT population
 - i. Data not currently available for use in the pediatric SOT population
6. Antifungal agents
- a. Nystatin
 - i. Dose for prophylaxis: 200,000–500,000 units swish and swallow three or four times daily
 - ii. Prophylaxis for *Candida* spp. (oral thrush)
 - b. Clotrimazole
 - i. Dose for prophylaxis: 10-mg troche dissolved by mouth two to four times daily
 - ii. Alternative for nystatin
 - iii. Prophylaxis for *Candida* spp.
 - iv. Drug interaction: May increase the blood concentration of CNIs and mTOR inhibitors.
 - c. Fluconazole
 - i. May be used for select patients for prophylaxis for *Candida* spp.
 - (a) For example:
 - (1) High-risk liver transplants with repeated operation, longer operation time, high transfusion requirement at the time of surgery, or renal failure
 - (2) Patients intolerant of nystatin or clotrimazole
 - (3) Patients requiring a pharmacologic method to increase CNI or mTOR inhibitor blood concentrations (“boosting”)
 - (b) Duration: often 4 weeks or more
 - ii. May be used for prophylaxis of *Coccidioides immitis* for patients who have a history of coccidioidomycosis or who are seropositive for *Coccidioides* spp. before transplantation. Duration: Prolonged (6–12 months) to lifelong
 - iii. Drug interaction: Fluconazole increases the blood concentration of CNIs and mTOR inhibitors.
 - d. Itraconazole, isavuconazole, or voriconazole with or without inhaled amphotericin B
 - i. Used for lung transplant recipients for *Aspergillus* spp. and *Candida* spp. prophylaxis.
 - ii. Duration: 4–6 months depending on risk, but may be continued up to lifelong

- iii. Drug interaction: Itraconazole and voriconazole significantly increase the blood concentration of CNIs and mTOR inhibitors.
 - (a) Recommended to decrease tacrolimus dose by 66% when voriconazole is initiated.
 - (b) Recommended to decrease cyclosporine dose by 50% when voriconazole is initiated.
- iv. Consider TDM for itraconazole and voriconazole.

Patient Cases

5. A.P. is 16-year-old Hispanic female patient with ESRD caused by systemic lupus erythematosus nephritis who is postoperative day 0 from a living donor kidney transplant. A.P. has been on hemodialysis for the past year. In her pretransplant serology screening, A.P. was noted to have a positive *Coccidioides* IgG ELISA (enzyme-linked immunosorbent assay) (1.8). A.P. currently lives in the southwestern United States. A.P. received standard basiliximab induction and will receive triple-maintenance immunosuppression with tacrolimus, mycophenolate sodium, and CCS. Which agent would be most appropriate for antifungal prophylaxis for A.P?
 - A. Nystatin suspension
 - B. Fluconazole tablets
 - C. No prophylaxis required.
 - D. Intravenous micafungin
6. E.E. is a 2-year-old white female patient with a medical history of biliary atresia who is postoperative day 0 from a deceased donor liver transplant. The patient has a documented sulfa allergy (hives). According to the transplant center protocol, the patient will receive atovaquone. Which is the most accurate statement regarding this alternative?
 - A. Although sulfamethoxazole/trimethoprim is available in a liquid formulation, atovaquone is only available as a tablet.
 - B. Both sulfamethoxazole/trimethoprim and atovaquone are effective at preventing *P. jiroveci* and *T. gondii*.
 - C. Atovaquone should be administered on an empty stomach.
 - D. Atovaquone is generally not recommended in patients with glucose-6-phosphate dehydrogenase deficiencies.

D. Immunizations

1. Pretransplant considerations: Patients should be up to date on all vaccines before transplantation, according to the Centers for Disease Control and Prevention (CDC) guideline and the 2013 Infectious Diseases Society of America (IDSA) clinical practice guideline for vaccination of the immunocompromised host, if possible.
 - a. Increased chance of immunologic response compared with posttransplantation
 - b. In some cases, accelerated schedules could be used. For example, as suggested in the 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host, the second dose of the measles, mumps, and rubella vaccine (MMR) and varicella vaccine may be given before 4 years of age, provided at least 4 weeks have elapsed since first dose administration. The two doses of the varicella vaccine optimally should be administered 3 months apart or more, if possible.
 - c. If possible, potential SOT should be delayed by 4 weeks or more from live vaccine administration, although the risks and benefits of earlier transplantation should be assessed with each individual patient.

- d. According to the 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host, potential SOT will be delayed by 2 weeks or more from inactivated vaccine administration, if possible, although the risks and benefits of earlier transplantation should be assessed with each individual patient.
 - e. Pneumococcal polysaccharide vaccine 23-valent (PPSV23): 2022 CDC guidelines for high-risk populations, specific to end-stage organ disease and SOT
 - i. One dose recommended for pediatric patients 2–18 years of age with chronic heart disease or chronic lung disease.
 - ii. One dose recommended for pediatric patients 6–18 years of age with chronic liver disease.
 - iii. Two doses, spaced 5 years apart, are recommended for pediatric patients 2–18 years of age who are SOT recipients, who have chronic renal failure, or who have nephrotic syndrome.
 - f. Pneumococcal conjugate vaccine (PCV13): 2022 CDC guidelines for high-risk populations, specific to end-stage organ disease and SOT
 - i. For patients 2–5 years of age with chronic renal failure, nephrotic syndrome, chronic lung disease, chronic heart disease, or SOT:
 - (a) Give one dose of PCV13 if three doses of PCV13 were previously received.
 - (b) Give two doses of PCV13, 8 weeks or more apart, if two or fewer doses of PCV13 were previously received.
 - ii. For patients 6–18 years of age with chronic renal failure, nephrotic syndrome, chronic lung disease, chronic heart disease, or SOT: Give one dose of PCV13 if no doses have been received previously.
 - g. Both PCV15 and PCV20 were approved in 2021, but these are limited to use in the adult population.
2. Posttransplant considerations
- a. As recommended in the 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host, patients may resume standard inactivated immunization schedule as recommended by the CDC 2–6 months after the organ transplant (6 months after transplantation would be preferable).
 - i. It is preferred, because of lack of response, that patients not receive inactivated vaccines during times of intensified immunosuppression, including the first 2 months posttransplantation.
 - ii. One exception would be that the inactivated influenza vaccine might be given after the first month posttransplantation in a community influenza outbreak.
 - b. Live virus vaccines should typically be avoided posttransplantation, including:
 - i. Varicella
 - ii. MMR
 - iii. Live attenuated influenza
 - iv. Rotavirus
 - v. Vaccinia (smallpox)
 - vi. Yellow fever
 - vii. *Vibrio cholerae*
 - viii. Typhoid (Vivotif Berna only)
 - ix. MMR and varicella-zoster virus may be considered in certain transplant recipients on reduced immunosuppression (Pediatr Transplant 2019;23:e13571)

Patient Cases

7. C.C. is a 16-year-old African American female patient with ESRD caused by focal segmental glomerulosclerosis. She had a peritoneal dialysis catheter placed 2 weeks ago and is in the clinic today for a pharmacotherapy pre-kidney transplant evaluation. C.C. has no other diagnosed chronic diseases or other major surgical procedures. Her vaccine records are as follows:

- Three doses of hepatitis B vaccine, with a recent hepatitis B surface antibody of 60 mIU/mL
- One dose of Tdap (tetanus diphtheria, and acellular pertussis) vaccine when the patient was 11 years old
- One dose of PCV13 when the patient was 15 years old
- Three doses of *Haemophilus influenzae* type b vaccine, with all doses received before 6 months of age
- Four doses of inactive polio vaccine
- Two doses of meningococcal vaccine, one at 11 years of age and one at 16 years of age
- Two doses of MMR vaccine
- Two doses of varicella vaccine
- One dose of influenza vaccine during the most recent influenza season
- Three doses of human papillomavirus 4 vaccine

Which would be best for C.C. to receive to ensure that she is up to date on vaccinations according to the CDC guidelines?

- A. PCV13 x 1
- B. Hepatitis B vaccine x 1
- C. PPSV23 x 1 now and repeat in 5 years
- D. *H. influenzae* type b vaccine x 1

8. K.C. is a 5-year-old white female patient who received a heart transplant 9 months ago for congenital heart disease. She is currently receiving tacrolimus, mycophenolate mofetil, and prednisolone for maintenance immunosuppression. On review of her immunization records, it is noted that she is due for the MMR vaccine, varicella vaccine, influenza vaccine, and diphtheria, tetanus, and acellular pertussis (DTaP). Which vaccine would be most appropriate for her to receive?

- A. MMR vaccine
- B. Varicella vaccine
- C. Intranasal influenza vaccine
- D. DTaP vaccine

XIX. OTHER CONSIDERATIONS AFTER TRANSPLANTATION

- A. Posttransplant Diabetes Mellitus
 - 1. Formerly NODAT (new-onset diabetes after transplantation)
 - 2. 3-year incidence in pediatric kidney transplant recipients is about 7%.
 - 3. Risk factors in pediatric kidney transplant recipients
 - a. BMI (body mass index) greater than 30 kg/m²
 - b. Tacrolimus use
 - c. Increased age at transplantation
 - d. Positive donor CMV antibody status with a recipient who had a negative CMV antibody status

4. Risk factors in pediatric liver transplant recipients
 - a. Age older than 5 years at transplantation
 - b. Cholestatic liver disease (except biliary atresia)
 - c. Hispanic race
 - d. CCS use
 - e. Tacrolimus use
 5. Mechanism
 - a. CNIs (more so with tacrolimus) directly toxic to pancreatic β cells
 - b. CCS increase insulin resistance.
 6. Treatment
 - a. Lifestyle modification through diet and exercise essential
 - b. In some cases, modification of the immunosuppressive regimen may be an option.
 - c. Patients may require insulin therapy.
 - d. Oral therapy: Use caution with metformin use, especially in the setting of unstable renal function and in patients with a history of lactic acidosis.
- B. Growth Concerns
1. End-stage organ disease often leads to linear growth impairment.
 - a. Kidney: Growth impaired because of malnutrition, growth hormone resistance, renal osteodystrophy, and metabolic acidosis.
 - b. Liver: Growth impaired because of malnutrition and growth hormone resistance.
 - c. Heart: Linear growth impairment does not appear to be as much of an issue as in other pretransplant patients.
 - d. Lung: One of the more common pediatric indications for lung transplantation is cystic fibrosis, causing growth impairment because of malabsorption, increased energy requirements, and decreased appetite.
 - e. Intestine: Growth impaired because of malnutrition.
 2. Often, organ transplantation improves linear growth but typically does not maximize catch-up growth; CCS may contribute to the inability to maximize catch-up growth.
 3. Management of growth recovery posttransplantation
 - a. Adequate nutrition
 - b. Minimize CCS exposure, if possible.
 - c. Correct metabolic acidosis, if present.
 - d. Recombinant human growth hormone
 - i. Concerns regarding SOT rejection and recombinant human growth hormone have not been validated; however, generally avoided in lung transplant recipients because of the possible association with the development of bronchiolitis obliterans in patients who received recombinant human growth hormone.
 - ii. May be indicated if the patient is less than 5% height-for-age (based on sex); other possible causes should first be corrected, if possible.
- C. Adherence
1. Possible consequences of nonadherence
 - a. Organ rejection (acute and chronic)
 - b. Worsening overall health
 - c. Decline in quality of life
 - d. Loss of transplanted organ
 - e. Increased health care costs
 - f. Death, especially in non-renal transplant recipients, where there are no dialysis-like alternatives

2. Factors affecting adherence
 - a. Patient-specific factors
 - i. Including support system of family and friends
 - ii. Engaging in risky behaviors may be a response to specific social situations.
 - b. Socioeconomic factors
 - c. Drug/disease-specific factors (including adverse drug effects): High pill burden
 - d. Health care setting and access to care
 - e. Provider-patient/caregiver dynamics
 3. Strategies to improve adherence
 - a. Implementing behavioral strategies
 - i. Simplify medications regimen, if possible.
 - ii. Use of medication box
 - iii. Use medications with longer durations, if possible.
 - iv. Use text message reminders and alarms or applications available for smartphones.
 - v. Work with individual patients on best strategy to fit medication schedule into his or her personal schedule.
 - b. Establishing a trusting relationship with patient, caretakers, and health care team
 - c. Ongoing education and evaluation regarding medication regimen
 - i. Use various forms of educational material, including written, verbal, and pictorial means.
 - ii. Provide patient-specific medication lists: Several programs available online.
 - d. Creating a social and health care provider support system
 - i. Patient involvement in transplant patient support groups
 - ii. Continuity of care with health care team
- D. Transition
1. Those in the adolescent and young adult years are at high risk of transplant complications. In renal transplant recipients, adolescents and young adults have the highest rates of acute rejection and loss of transplanted organ.
 2. Recommendations for transitioning from pediatric to adult transplant care
 - a. Approach transition as a gradual process as opposed to a sudden transfer.
 - b. Educate and prepare the patient and caregivers early regarding the transition process.
 - c. Use checklists to assess the patient's progress and knowledge.
- E. Malignancy
1. Overimmunosuppression increases the risk of developing malignancies.
 - a. Decreased immune response to oncogenes
 - b. Increased reactivation of latent viruses
 2. PTLD
 - a. Most common malignancy post-pediatric SOT; accounts for about 50% of posttransplant malignancies.
 - b. Most pediatric cases of PTLD are associated with EBV, which generally infects B cells.
 - i. In immunocompetent individuals, EBV-infected B-cell proliferation is controlled by CD4⁺ T cells, CD8⁺ T cells, and NK cells.
 - ii. In patients with T-cell response impairment, such as SOT recipients, uncontrolled proliferation of EBV-infected B cells may occur and lead to PTLD.
 - c. Risk reported as 5%–10% for pediatric SOT patients.
 - d. Treatment
 - i. Reduction in immunosuppression often first-line therapy for PTLD.

Patient Cases

9. H.P. is an 8-year-old male patient from India who received a deceased donor kidney transplant 5 years ago for ESRD caused by posterior urethral valves and dysplastic kidneys. H.P. is being seen today in the pediatric renal transplant clinic. Of note, H.P. was treated 4 months ago with high-dose CCS for mild acute cellular rejection caused by medication nonadherence. H.P.'s current height is 114.4 cm, which is below the 5th percentile height-for-age. The patient has been below the 5th percentile height-for-age for more than 1 year. H.P.'s weight is 34.9 kg, which is in the 95th percentile weight-for-age. According to the transplant dietitian, the patient has been receiving adequate nutrition for the past year. H.P.'s laboratory results for today are as follows: Na 138 mEq/L, K 4.4 mEq/L, Cl 105 mEq/L, HCO_3^- 26 mEq/L, BUN 12 mg/dL, SCr 0.34 mg/dL, and glucose 86 mg/dL. H.P. currently takes tacrolimus 0.6 mg by mouth twice daily, prednisolone 3 mg by mouth daily, sodium bicarbonate 650 mg by mouth three times daily, amlodipine 2.5 mg by mouth daily, 1 sulfamethoxazole/trimethoprim 400/80 mg tablet by mouth daily, and magnesium oxide 400 mg by mouth twice daily. Which statement is most appropriate?
- A. H.P. should not be initiated on recombinant human growth hormone because it increases the risk of acute rejection in pediatric kidney transplant recipients.
 - B. H.P. should not be initiated on recombinant human growth hormone because he is currently being treated for metabolic acidosis with sodium bicarbonate.
 - C. H.P. should be initiated on recombinant human growth hormone because his metabolic acidosis is currently treated, he is not malnourished, and he is maintained on low-dose CCSs.
 - D. H.P. should be initiated on recombinant human growth hormone and have prednisolone and sodium bicarbonate discontinued.
10. C.P. is a 16-year-old white female patient who presents after a living unrelated donor kidney transplant 1 year ago because of ESRD caused by autosomal recessive polycystic kidney disease. Several members of the transplant team have expressed concern for recent medication nonadherence because her tacrolimus trough concentrations have been highly variable at clinic visits and are often undetectable. C.P. and her family are meeting today with the transplant team to discuss the team's concerns. Her medications are as follows:
- Isradipine 5-mg capsule by mouth every 6 hours as needed for blood pressure greater than 150/90 mm Hg
 - Prednisone 5 mg by mouth daily at 8 a.m.
 - Tacrolimus 3 mg by mouth twice daily at 8 a.m. and 8 p.m.
 - Pantoprazole 40 mg by mouth daily at 8 a.m.
 - Amlodipine 10 mg by mouth daily at 8 a.m.
 - Atenolol 50 mg by mouth daily at 8 p.m.
 - Cetirizine 10 mg by mouth daily at 8 a.m.
- Which strategy would most likely increase medication adherence?
- A. Switching from tacrolimus to tacrolimus extended release 6 mg by mouth at 8 a.m. and switching the timing of atenolol to 8 a.m.
 - B. Switching from using a medication box to using individual prescription bottles.
 - C. Switching from tacrolimus twice daily to tacrolimus 2 mg by mouth three times daily.
 - D. Explaining to C.P. and her family that missing medications, as she is intentionally doing, is unacceptable, and that she will lose her kidney transplant if this continues.

- ii. For PTLTD refractory to reduction in immunosuppression, antiviral therapy (ganciclovir) and rituximab have been used.
 - iii. Chemotherapy may be used for resistant PTLTD.
- 3. Other malignancies
 - a. Skin cancer
 - b. Gynecologic malignancy
 - c. Kaposi sarcoma: Associated with human herpesvirus 8.
 - d. Sarcoma
 - e. Thyroid cancer
- F. Ulcer Prophylaxis
 - 1. Primarily implemented because of large CCS burden.
 - 2. Proton pump inhibitors or histamine-2 antagonists may be used. Increasing adult reports that proton pump inhibitors are associated with increased risk of chronic kidney disease.
- G. Hypertension
 - 1. Medications that increase the risk of hypertension
 - a. CNIs
 - b. CCS
 - 2. Management
 - a. Lifestyle modification
 - b. Adjust immunosuppressive regimen, if possible. Some programs use a steroid withdrawal or minimization protocol or CNI minimization protocols.
 - c. Antihypertensive agents: Most antihypertensive agents may be used posttransplantation.
 - i. Use caution with CYP3A4 interactions: Nicardipine, diltiazem, and verapamil.
 - ii. Typically avoid ACE (angiotensin-converting enzyme) inhibitors immediately post-kidney transplantation.
 - (a) Because of the increase in SCr, can mask true renal function.
 - (b) Risk of hyperkalemia
- H. Hyperlipidemia
 - 1. Medications that increase the risk of hyperlipidemia
 - a. CNIs
 - b. mTOR inhibitors
 - c. CCS
 - 2. Agents typically recommended for transplant patients because of less interaction with CNIs: Atorvastatin, rosuvastatin, and pravastatin
 - 3. Agents typically avoided with transplant patients because of more interaction with CNIs: Simvastatin, lovastatin, and pitavastatin

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

For diarrhea caused by intestinal inflammation, blood concentrations of tacrolimus may increase because the activity of both CYP3A and P-glycoprotein, which are substrates for tacrolimus, is decreased in the setting of intestinal inflammation (Answer C is correct). Although switching from brand-name tacrolimus to a generic may slightly alter the tacrolimus concentration, the difference in drug exposure of brand tacrolimus to generic tacrolimus by Sandoz is less than 10% (Answer A is incorrect). Tacrolimus rate and extent of absorption can be decreased when tacrolimus is administered with food (especially food with high fat content) with oral formulations; thus, increasing the enteral intake could potentially lead to decreased tacrolimus trough concentrations (Answer B is incorrect). The half-life of tacrolimus is about 12 hours in pediatric patients; thus, the effects of an extra dose 2 weeks ago would be negligible (Answer D is incorrect).

2. Answer: B

The 2009 KDIGO guidelines recommend using induction, in the form of a biologic agent, for kidney transplant recipients (Answer C is incorrect). Basiliximab is the recommended agent for patients who are not considered at high immunologic risk. The guidelines suggest using ATG, rather than basiliximab, for kidney transplant recipients at high risk of acute rejection, as this patient would be considered (Answer B is correct; Answer D is incorrect). Risk factors that factor into a patient's being at high risk of acute rejection include increased number of HLA mismatches, young recipient age, older donor age, African American ethnicity, ABO incompatibility, delayed onset of kidney function, cold ischemic time greater than 24 hours, PRA greater than 0%, and presence of DSA. In addition, ATG may decrease the risk of IgA nephropathy recurrence post-transplantation. Rituximab has not been shown to be effective over placebo when used as a single induction agent (Answer A is incorrect).

3. Answer: D

Only a few small, randomized controlled trials exist evaluating strategies to treat acute AMR in kidney transplantation. The 2009 KDIGO guidelines recommend one or a combination of the following to treat acute AMR with or without CCS: (1) plasmapheresis,

(2) IVIG, (3) rituximab, and (4) lymphocyte-depleting agent (e.g., ATG) (Answer D is correct). Basiliximab is used only as an induction agent (Answer A is incorrect). Intravenous methylprednisolone may be used in a regimen to treat acute AMR, but it should not be used as a single agent (Answer B is incorrect). Eculizumab has been used to treat multidrug-resistant acute AMR, but no randomized controlled trials currently exist to validate the efficacy of eculizumab for this indication (Answer C incorrect).

4. Answer: A

Reduction in immunosuppression is recommended for first-line preemptive management if the patient has a rapidly increasing EBV viral load (e.g., a 10-fold or greater increase in plasma EBV PCR) (Answer A is correct). Currently, the efficacy of antiviral therapy (acyclovir, ganciclovir, and valganciclovir) with or without IVIG (intravenous immunoglobulin) or rituximab has not been validated for preemptive PTLT management (Answers B and D are incorrect). Arginine butyrate has been used in small investigational studies for confirmed PTLT; however, this agent is not commercially available in the United States (Answer C is incorrect). Arginine butyrate induces the lytic cycle of EBV, allowing EBV-infected cells to be more susceptible to ganciclovir.

5. Answer: B

The 2013 American Society of Transplantation infectious disease guidelines recommend fluconazole prophylaxis for all transplant recipients with a history of *Coccidioides* spp. infection or pretransplant *Coccidioides* spp. serologies for 6–12 months post-transplantation up to lifelong (Answer B is correct and Answer C is incorrect). Nystatin suspension is not recommended because of its poor absorption from the GI tract (Answer A is incorrect). And echinocandins have variable in vitro activity against *Coccidioides* spp.; thus, their use is not recommended (Answer D incorrect).

6. Answer: B

According to the 2013 American Society of Transplantation infectious disease guidelines, although sulfamethoxazole/trimethoprim is the preferred agent for *P. jiroveci* and *T. gondii*, atovaquone is an acceptable alternative for patients who cannot tolerate

sulfamethoxazole/trimethoprim (Answer B is correct). Atovaquone is only available as a 750 mg/5 mL suspension, whereas sulfamethoxazole/trimethoprim is available as a tablet, suspension, and intravenous injectable (Answer A is incorrect). It is recommended that atovaquone be administered with meals because fatty foods increase the absorption of atovaquone (Answer C is incorrect). Dapsone, not atovaquone, is generally contraindicated in patients with glucose-6-phosphate dehydrogenase deficiencies (Answer D is incorrect).

7. Answer: C

Two doses of PPSV23, spaced 5 years apart, are recommended for pediatric patients 2–18 years of age who are SOT recipients or who have chronic renal failure (Answer C is correct). For children 6 years and older with chronic kidney disease, only one dose of PCV13 is indicated (Answer A is incorrect). This patient has completed the recommended three-dose series of the hepatitis B vaccine, and her hepatitis B surface antibody is positive (10 mIU/mL or greater) (Answer B is incorrect). The *H. influenzae* type b vaccine is not indicated in patients 5 years and older unless they have asplenia or HIV infection (Answer D is incorrect).

8. Answer: D

Patients may resume a standard inactivated immunization schedule as recommended by the CDC 2–6 months after the organ transplant (although 6 months after transplantation would be preferable). Live vaccinations should be avoided after SOT. The DTaP vaccine is an inactivated vaccine; thus, it would be safe to give to this patient (Answer D is correct). The MMR, varicella, and intranasal (live attenuated) influenza vaccines are all live vaccines and should be avoided (Answers A–C are incorrect). This patient could receive the inactivated influenza vaccine injection, when indicated.

9. Answer: C

Recombinant human growth hormone should be considered if a patient is below the 5th percentile of height-for-age, assuming that the patient does not have untreated, or inadequately treated, metabolic acidosis and is receiving a low-dose CCS (Answer C is correct, and Answer B is incorrect). Historical concerns regarding kidney transplant rejection and recombinant human growth hormone have not been validated and should not be a reason to avoid initiating therapy if the patient

is closely followed (Answer A is incorrect). Although discontinuing CCS to improve growth in a patient with fairly recent acute cellular rejection may be debated among transplant experts, this patient should not have sodium bicarbonate discontinued because his metabolic acidosis is currently adequately treated (Answer D is incorrect).

10. Answer: A

It has been shown that patients with chronic diseases are more adherent to once-daily medication regimens than to regimens administered more often. Extended-release tacrolimus, the once-daily formulation, is approved for kidney transplant recipients who are 16 years and older and converted on an equal daily milligram dose from immediate-release tacrolimus. Timing all medications once daily at 8 a.m. should help with medication adherence, provided this time is agreed on in active discussion with the patient and her family (Answer A is correct). Use of medication boxes often assists with medication adherence and simplifies medication regimens compared with individual prescription bottles (Answer B is incorrect). Thrice-daily dosing is associated with lower rates of adherence than is less-frequent dosing (Answer C is incorrect). Finally, it is essential to have a trusting relationship with the patient, caretakers, and health care team. Accusing the patient of intentionally being nonadherent could jeopardize this trusting relationship, potentially further damaging current her health care adherence (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

Tacrolimus rate and extent of absorption can be decreased when tacrolimus is administered with food (especially food with high fat content) with oral formulations; thus, consistency of administration with or without food is essential. The half-life of tacrolimus is about 12 hours in pediatric patients; thus, this patient should be at steady state on tacrolimus because her routine changed 96 hours ago (Answer B correct). Amlodipine does not typically have a direct drug interaction with tacrolimus (Answer A incorrect). Other calcium channel blockers, including diltiazem, verapamil, and nifedipine, act as CYP3A4 inhibitors, increasing tacrolimus trough concentrations. Although vomiting doses of tacrolimus can decrease tacrolimus trough concentrations, this patient should be at the same steady state, if no other changes have been made, because the episode of vomiting occurred 5 days ago (Answer C is incorrect). Atorvastatin and tacrolimus do not appear to have a significant drug interaction (Answer D is incorrect), although interactions with CNIs increasing the systemic exposure of other statins have been documented.

2. Answer: A

Premedications are typically recommended for lymphocyte-depleting agents. Cell destruction is often associated with widespread cytokine release leading to significant adverse effects, including chills, headache, nausea, fever, diarrhea, and malaise. Alemtuzumab, rATG, and rituximab are all lymphocyte-depleting agents (Answers B–D are incorrect). Basiliximab is a non-depleting agent that antagonizes the IL-2 receptor (Answer A is correct).

3. Answer: B

The package insert for rATG with kidney transplant recipients recommends decreasing the dose by 50% when the WBC is between 2×10^3 cells/mm³ and 3×10^3 cells/mm³ and holding the dose if the WBC is less than 2×10^3 cells/mm³. The package insert also recommends decreasing the dose by 50% when the platelet count is 50,000–70,000/mm³ and holding the dose if the platelet count is less than 50,000/mm³ given the patient's platelet count (Answers A, C, and D are incorrect; Answer B is correct).

4. Answer: B

The package insert for voriconazole recommends decreasing the tacrolimus dose by 66% when voriconazole is initiated. This same strategy is applicable when voriconazole is discontinued (Answer B is correct, and Answers A, C, and D are incorrect). The package insert for voriconazole recommends decreasing the cyclosporine dose by 50% when voriconazole is initiated.

5. Answer: C

Mycophenolate formulations are associated with GI toxicity and pancytopenia (Answer C is correct). Mycophenolate is not nephrotoxic (Answer B is incorrect). Mammalian target of rapamycin (mTOR) inhibitors (e.g., sirolimus, everolimus) are associated with delayed wound healing, hyperlipidemia, oral ulcers, edema, bone marrow suppression, and pneumonitis (Answer A is incorrect). Valganciclovir is typically associated with pancytopenia and nephrotoxicity. Tacrolimus is associated with hyperglycemia, neurotoxicity, nephrotoxicity, hypertension, and alopecia (Answer D is incorrect).

6. Answer: B

The daily oral dose of cyclosporine is typically 3 times the intravenous daily dose of oral cyclosporine because the bioavailability of cyclosporine is about 33%. Thus, to convert cyclosporine-modified capsules (Neoral) 100 mg by mouth twice daily, use $200 \text{ mg oral daily} \times 0.3 = 66.7 \text{ mg intravenous cyclosporine daily}$; $66.7 \text{ mg/day} \times 1 \text{ day/24 hours} = 2.8 \text{ mg/hour intravenous cyclosporine}$ (Answer B is correct and Answers A, C, and D incorrect).

7. Answer: D

Cyclosporine is a substrate of CYP3A4. Micafungin does not interfere with CYP3A4 and is not associated with nephrotoxicity (Answer D is correct). Itraconazole and voriconazole are potent CYP3A4 inhibitors and have the potential to drastically increase the cyclosporine blood concentrations (Answers A and C are incorrect). Amphotericin B is highly nephrotoxic and may cause additive nephrotoxicity with CNIs (Answer B is incorrect).

8. Answer: A

Tacrolimus requires close TDM because there is a narrow window between appropriate therapeutic effects and potentially toxic concentrations. Because of this, tacrolimus is often classified as an NTI drug. Tacrolimus trough concentrations correlate well with overall drug exposure (Answer A is correct). Although some pediatric centers follow ganciclovir concentrations for patients taking valganciclovir, this is not common practice and is not commonly recommended (Answer B is incorrect). Mycophenolate mofetil TDM is challenging because mycophenolic acid trough concentrations are not reliable for making dose adjustments unless a patient is extremely overdosed. Accurate pharmacokinetic monitoring requires measuring mycophenolic acid concentrations at several time points; thus, mycophenolic acid is often not feasible for pediatric patients (Answer C is incorrect). rATG does not have standard drug concentration monitoring (Answer D is incorrect), but WBC, platelet count, and lymphocyte count should be monitored while a patient is receiving infusions.

9. Answer: A

Almost all pediatric liver transplant patients in the United States will be initiated on a tacrolimus-based regimen. Immediate-release tacrolimus (Prograf) is approved for pediatric liver transplant recipients (Answer A is correct). Extended-release tacrolimus (Astagraf) is currently approved only for kidney transplant recipients (Answer D is incorrect). Belatacept is not approved for pediatric SOT recipients, primarily because there is an increased rate of PTLT in patients who are EBV IgG negative (because many pediatric patients are EBV IgG negative) (Answer B is incorrect). Sirolimus has an FDA black box warning for increased rates of hepatic artery thrombosis in liver transplant recipients who were initiated on sirolimus at transplantation (Answer C is incorrect). In addition, sirolimus is associated with delayed wound healing.

10. Answer: D

Patients receiving ecilizumab infusions are at an increased risk of infections, especially by encapsulated bacteria. Specifically, it is recommended to give the quadrivalent meningococcal conjugate vaccine 2 weeks before initiating ecilizumab therapy (Answer D is correct). The ecilizumab package insert recommends supplemental dosing of ecilizumab after plasmapheresis,

plasma exchange, and fresh frozen plasma infusions (Answer A is incorrect). Supplemental doses of ecilizumab are not routinely recommended after hemodialysis, primarily because of the molecular size of ecilizumab (Answer B is incorrect). Ecilizumab is only available through a restricted program, which requires providers to enroll in a REMS program, not the facility administering ecilizumab (Answer C is incorrect).

11. Answer: A

The 2019 American Society of Transplantation infectious disease guidelines recommend reducing immunosuppression as first-line therapy for treatment of BK PyVAN (Answer A is correct). Recommended targets for immunosuppression include tacrolimus trough concentrations less than 6 ng/mL, cyclosporine trough concentrations less than 150 ng/mL, sirolimus trough concentrations less than 6 ng/mL, and a mycophenolate mofetil daily dose of 50% of maintenance or less. J.P.'s tacrolimus dose should be decreased to target a lower tacrolimus trough concentration and/or his mycophenolate mofetil dose should be decreased to 500 mg by mouth twice daily. Use of antiviral therapies, including cidofovir and leflunomide, should be reserved for situations with a sustained high-level plasma BK load after an appropriate reduction in immunosuppression (Answers B and C are incorrect). Valganciclovir has no activity against polyomaviruses (Answer D is incorrect).

12. Answer: A

The 2019 American Society of Transplantation infectious disease guidelines recommend intravenous ganciclovir, followed by conversion to oral valganciclovir, when a high-risk pediatric patient is considered stable for CMV prophylaxis (Answer A is correct). Cytomegalovirus IVIG is used in combination with other antiviral therapies in some centers for CMV, although the data supporting this practice are limited. Cytomegalovirus IVIG should not be used alone for CMV prophylaxis (Answer B is incorrect). The guidelines do not recommend acyclovir for CMV prophylaxis because acyclovir does not have anti-CMV activity at commonly used doses (Answer C is incorrect). Cidofovir is not recommended for CMV prophylaxis because it is highly nephrotoxic (Answer D is incorrect). Brincidofovir is currently being investigated for treatment of CMV disease, but it is not currently commercially available in the United States.

13. Answer: D

Risk factors for developing PTDM in pediatric liver transplant recipients include age older than 5 years at transplantation, cholestatic liver disease (except biliary atresia), Hispanic race, CCS use, and tacrolimus use (Answer D is correct and Answers A–C are incorrect).

CARDIOLOGY

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CARDIOLOGY

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Learning Objectives

1. Develop strategies for the acute and long-term treatment of patients with a diagnosis of Kawasaki disease.
2. Discuss the pharmacologic agents used to manage the consequences associated with congenital heart diseases.
3. Determine appropriate first-line and alternative antihypertensive agents for the control of blood pressure in neonates, children, and adolescents.
4. Describe the pharmacologic management of the most commonly occurring arrhythmias in the pediatric population.
5. Determine appropriate pharmacologic agents for preventing and treating thrombosis in the pediatric population with cardiac disease.
6. Select the best therapeutic agent to manage acute and chronic pulmonary hypertension (PHN) in pediatric patients.

Abbreviations this Chapter

ACEI	Angiotensin-converting enzyme inhibitor
AF	Atrial flutter
Afib	Atrial fibrillation
AHA	American Heart Association
aPTT	Activated partial thromboplastin time
ARB	Angiotensin receptor blocker
AV	Atrioventricular
AVNRT	Atrioventricular nodal reentrant (junctional) tachycardia
AVRT	Atrioventricular reentrant (reciprocating) tachycardia
BNP	Brain natriuretic peptide
CAA	Coronary artery aneurysm
cGMP	Cyclic guanosine monophosphate
CHD	Congenital heart disease
CHF	Congestive heart failure
CoA	Coarctation of the aorta
CRP	C-reactive protein
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
ESR	Erythrocyte sedimentation rate
IVIG	Intravenous immune globulin
HLHS	Hypoplastic left heart syndrome
KD	Kawasaki disease
NT-proBNP	N-terminal pro-brain natriuretic peptide
PA	Pulmonary artery

PDA	Patent ductus arteriosus
PHN	Pulmonary hypertension
PVC	Premature ventricular contraction
SVT	Supraventricular tachycardia
TGA	Transposition of the great arteries
ToF	Tetralogy of Fallot
VF	Ventricular fibrillation
VSD	Ventricular septal defect
VT	Ventricular tachycardia
WPW	Wolff-Parkinson-White (syndrome)

Self-Assessment Questions

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

1. S.E. is a 1-year-old boy (weight 10.8 kg) who presents to the emergency department (ED) with a 4-day history of fever, bilateral nonpurulent conjunctivitis, cracked red lips, a diffuse maculopapular rash, and a cervical lymphadenopathy greater than 1.5 cm on the left side. According to his mother, his temperature has been 102°F–104°F (38.8°C–40°C). He has been extremely irritable, especially when febrile, with no runny nose or cough but some mild congestion. In the ED, serum chemistries are within normal limits; white blood cell count (WBC) is 10.4×10^3 cells/mm³, platelet count is 250,000/mm³, and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are markedly elevated. A chest radiograph is normal, and cultures of blood and urine, as well as viral swabs, are collected. Because of the child's physical examination, laboratory values, and 4-day history of fever, an echocardiogram (ECHO) is obtained, which reveals normal ejection fraction without evidence of coronary artery aneurysms (CAAs) or valvular regurgitation. At this point, which is best for treating S.E.?
 - A. Immune globulin 20 g once with high-dose aspirin, starting immediately.
 - B. Immune globulin 20 g once with high-dose aspirin after fever has persisted for 10 days or more.
 - C. No medications because this patient is not at risk of developing CAAs, according to the ECHO results.
 - D. Immune globulin 4 g once daily for 4 days with high-dose aspirin, starting immediately.

2. C.P. is a 2-year-old boy (weight 12 kg) treated for a diagnosis of Kawasaki disease (KD) 8 weeks ago. A repeat ECHO reveals an aneurysm greater than 8 mm in diameter in the proximal left anterior descending coronary artery with evidence of a small, nonocclusive coronary artery thrombosis. Which is the best treatment to initiate for C.P.?
- Low-dose aspirin until the aneurysm regresses.
 - Clopidogrel until the aneurysm regresses.
 - Low-dose aspirin with clopidogrel until the aneurysm regresses.
 - Low-dose aspirin with clopidogrel and warfarin indefinitely.
3. L.E. is a 2-month-old girl (weight 4 kg) with a diagnosis of a ventricular septal defect (VSD) shortly after birth. She is now being admitted to the hospital for failure-to-thrive. Blood pressure is within normal limits for age and sex. Average heart rate is 170 beats/minute. Chest radiograph reveals pulmonary edema and cardiomegaly. Left ventricular ejection fraction is 0.6 on ECHO. Patch closure of her VSD is planned, but the earliest her surgery can be scheduled is 2 months from now. Which medication regimen would be most appropriate for L.E. until her cardiac surgery?
- Digoxin, captopril, and propranolol.
 - Digoxin, captopril, and furosemide.
 - Captopril and furosemide.
 - Captopril, furosemide, and propranolol.
4. R.P. is an 8-year-old girl (height 51 inches [130 cm] [50th percentile for age], weight 39 kg [above 99th percentile for age]). Her average blood pressure readings from her past three visits to her primary care physician have been 112/73–113/74 mm Hg. Her family history is not significant for cardiovascular disease or diabetes mellitus, but her paternal and maternal grandmothers have hypertension. Serum chemistries are within normal limits. Her cholesterol panel is within normal limits except for mildly elevated triglycerides. Urinalysis is negative.

Blood Pressure Values for Girls by Age and Height Percentile			
Age (yr)	Blood Pressure (percentile)	Systolic Blood Pressure for 50th Percentile of Height (mm Hg)	Diastolic Blood Pressure for 50th Percentile of Height (mm Hg)
8	50th	97	59
	90th	110	72
	95th	113	74
	95th + 12 mm Hg	125	86

Data from: Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017;140:e20171904.

Which would be most appropriate for R.P. at this time?

- Give enalapril, and recheck blood pressure in 6 months.
 - Give amlodipine, and recheck blood pressure in 6 months.
 - Give no medication, and recheck blood pressure in 6 months.
 - Counsel for diet and physical activity, and order ambulatory blood pressure monitoring and diagnostic evaluation.
5. J.V. is an 11-year-old boy (height 59 inches [151.4 cm] [75th percentile], weight 48.1 kg [90th percentile]) with a history of end-stage renal disease secondary to bilateral cystic dysplasia of the kidneys. He had a cadaveric renal transplant 2 months ago, and because of neurogenic bladder, he has a nephrostomy and external pouch. He is being immunosuppressed with tacrolimus, mycophenolate, and prednisone. His average blood pressures during his past three visits to the clinic have been 132/91–134/93 mm Hg. Recent laboratory values are as follows: sodium 138 mEq/L, potassium 4.4 mEq/L, total chloride 104 mEq/L, CO₂ 27 mEq/L, BUN 8 mg/dL, and SCr 0.9 mg/dL. Complete blood cell count (CBC) is within normal limits, but urinalysis reveals slightly cloudy urine with protein 30 mg/dL, negative glucose, moderate blood, large leukocyte esterase, WBC 5.1–10.0 x 10³ cells/mm³, red blood cell (count) (RBC) 3–5 x 10³ cells/mm³, and moderate bacteria. He has no difficulty or pain with urination, has no leakage from the nephrostomy, and is afebrile.

Blood Pressure Values for Boys by Age and Height Percentile			
Age (yr)	Blood Pressure (percentile)	Systolic Blood Pressure for 75th Percentile of Height (mm Hg)	Diastolic Blood Pressure for 75th Percentile of Height (mm Hg)
11	50th	103	63
	90th	116	75
	95th	120	78
	95th + 12 mm Hg	132	90

Data from: Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017;140:e20171904.

Which would be best for treating J.V.?

- Give lisinopril, and recheck blood pressure at next clinic visit.
- Do not give antihypertensive because high blood pressure is desirable to ensure adequate perfusion of the transplanted kidney.
- Counsel for diet and physical activity, and recheck blood pressure at next clinic visit.
- Give amlodipine, and recheck blood pressure at next clinic visit.

Questions 6 and 7 pertain to the following case.

F.E. is a 14-year-old female adolescent who presents to the ED after her mother finds her unresponsive in the bathroom. She is currently awake and endorses chest pain and feeling like her heart is beating funny. On physical examination, she is tachycardic, but her other vital signs are stable. A complete metabolic panel is within normal limits, and a urine drug screen is negative. Electrocardiogram (ECG) reveals a corrected QT (QTc) of 580 milliseconds. According to F.E., she and her mother had been arguing just before the event. According to her mother, F.E. has a history of “fainting spells” when she gets upset and when she works out too much. Her mother says that F.E. is just being overly dramatic and not drinking enough water when she exercises. Cardiology is consulted to evaluate the patient.

- Which medication is F.E. most likely to be prescribed?
 - No medication, but she is counseled to avoid emotional triggers.

- Atenolol.
 - Digoxin.
 - Amiodarone.
- Which potentially fatal arrhythmia is most likely to develop in F.E.?
 - Atrioventricular reentrant (reciprocating) tachycardia (AVRT).
 - Pulseless electrical activity.
 - Complete heart block.
 - Torsades de pointes.
 - N.R. is a 10-year-old girl (weight 37 kg) with a history of congestive heart failure (CHF) who is admitted to the hospital for severe nausea, vomiting, and dehydration. She has a peripherally inserted central catheter placed for the administration of intravenous fluids because she keeps losing peripheral access. On day 5 of admission, she has arm swelling with pain and redness. Ultrasonography reveals an extensive thrombus. Enoxaparin 40 mg subcutaneously is initiated twice daily. Initial Plt is 125,000/mm³. After 2 days of therapy, the clot is continuing to expand, despite an anti-factor Xa (anti-Xa) of 1.02 units/mL. Her Plt has also decreased to 66,000/mm³. An anti-heparin antibody screen is positive. Which would be best for N.R.?
 - Increase the enoxaparin dose.
 - Change to unfractionated heparin.
 - Change to argatroban.
 - Continue enoxaparin at the same dose, and add warfarin.
 - W.K. is a 13-year-old male adolescent (weight 47 kg) who received a bioprosthetic aortic valve because of aortic valve insufficiency. His last ECHO before valve placement revealed an ejection fraction of 70%. He has never had dysrhythmias, and he has no history of coagulopathy. Which would be the best anticoagulation for W.K. after valve placement?
 - Warfarin with goal international normalized ratio (INR) 2.5–3.5 for 3 months, followed by low-dose aspirin for life.
 - Warfarin with goal INR 2–3 for 3 months, followed by low-dose aspirin for life.

-
- C. Warfarin with goal INR 2.5–3.5 for life.
- D. Warfarin with goal INR 2–3 for life.
10. G.S. is a 3-month-old girl (weight 3.4 kg, 32 weeks' gestational age, birth weight 1.5 kg) who received a diagnosis of truncus arteriosus and interrupted aortic arch. She went to the operating room for repair of the truncus arteriosus. Unfortunately, during surgery, she had a significant pulmonary hypertensive crisis with suprasystemic pulmonary artery (PA) pressures. She was initiated on inhaled nitric oxide at 20 ppm, given sodium bicarbonate, and briefly hyperventilated. Her PA pressures were lowered, and she was transported to the pediatric intensive care unit (ICU). During the first few hours in the ICU, her PA pressures began to rise and became equal to her systemic pressures. Which would be the most appropriate adjustment to G.S.'s therapy at this time?
- A. Increase inhaled nitric oxide above 20 ppm indefinitely.
- B. Discontinue inhaled nitric oxide, and initiate inhaled iloprost.
- C. Continue inhaled nitric oxide at 20 ppm, and initiate oral sildenafil.
- D. Continue inhaled nitric oxide at 20 ppm, and initiate intravenous epoprostenol.
11. K.W. is a 13-month-old boy (weight 9.4 kg) with a history significant for a previously repaired large VSD and pulmonary hypertension (PHN). He has been maintained on sildenafil 15 mg orally four times daily and bosentan 15.6 mg orally twice daily. Before starting sildenafil and bosentan therapy, his baseline alanine aminotransferase (ALT) was 42 IU/L, and his aspartate aminotransferase (AST) was 30 IU/L. Repeat ALT and AST values after 2 months of sildenafil and bosentan therapy are 500 IU/L and 750 IU/L, respectively. He has had recent nausea, vomiting, and fatigue, but no jaundice. Which would be the best treatment for K.W.?
- A. Continue sildenafil and bosentan at the same doses.
- B. Continue sildenafil at the same dose, and discontinue bosentan.
- C. Reduce the sildenafil and bosentan doses.
- D. Continue sildenafil at the same dose, and reduce the bosentan dose.
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BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.9
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.2, 2.4, 2.5
3. Domain 3: Information Management, Research, and Education; Task(s): 3.1, 3.2
4. Domain 4: Public Health and Patient Advocacy; Task(s): 4.3

I. KAWASAKI DISEASE

A. Epidemiology

1. KD is an acute vasculitis that occurs in children worldwide, but the annual incidence is highest in Asian countries, most notably Japan and the Pacific Islands.
2. The disease predominantly affects children younger than 5 years.
3. In the United States, KD is the leading cause of acquired heart disease in children. Death related to myocardial ischemia and infarction may occur many years later in patients who had CAAs or stenoses, as well as in patients who were not given this diagnosis initially and were treated accordingly.

B. Etiology – Cause unknown, but an infectious source is usually suspected

C. Clinical Phases of Illness

1. The acute phase of illness starts with the onset of fever and ends with fever resolution.
2. The subacute phase starts with resolution of fever and ends when other clinical features resolve. This phase typically begins about 10 days into the illness and lasts for about 2 weeks. Periungual peeling of the fingers and toes, as well as thrombocytosis, occurs during this phase.
3. The convalescent phase starts when clinical features have resolved and ends when ESR and Plt have returned to normal. This phase may last 4–8 weeks after onset of illness.

D. Diagnosis

1. No single diagnostic test for KD; diagnosis of exclusion (particularly infections)
2. Clinical, laboratory, and cardiac features
 - a. Principal clinical findings (“CRASH and Burn” – “C” = conjunctivitis, “R” = rash, “A” = adenopathy, “S” = strawberry tongue, “H” = hands and feet; burn for fever)
 - i. A nonexudative, bilateral conjunctivitis that develops shortly after onset of fever is one of the most common clinical findings.
 - ii. Development of a rash is common within 5 days of onset of fever and is usually a diffuse maculopapular rash that involves the trunk and extremities.
 - iii. Cervical lymphadenopathy is the least common of the principal findings. It is usually unilateral and involves at least one lymph node that is firm, nonfluctuant, and greater than 1.5 cm in diameter.
 - iv. Oropharyngeal involvement is common and includes dryness, cracking, and peeling of the lips; erythema of the lips and oropharyngeal mucosa; and “strawberry tongue.”
 - v. Erythema and/or edema of the palms and soles may occur during the acute phase of the illness, with periungual desquamation of fingers and toes occurring in the subacute phase.
 - vi. Temperature is typically high, spiking (102°F–104°F [38.9°C–40°C]), and remittent. Fever generally does not respond to antibiotics and may not respond to antipyretics.
 - b. Other clinical findings involve the musculoskeletal system (arthritis/arthritis involving several joints), central nervous system (CNS) (extreme irritability, sensorineural hearing loss), and gastrointestinal (GI) tract (diarrhea, vomiting, abdominal pain, liver enlargement and jaundice, hydrops of the gallbladder).
 - c. Laboratory findings
 - i. ESR and CRP not specific but almost always increased
 - ii. Thrombocytosis generally not present in acute phase of illness, but usually occurs in subacute phase. Leukopenia and thrombocytopenia are rare in KD (considered a risk factor for CAA if low Plt initially).

-
- d. Cardiac findings
 - i. ECHO is a critical part of the evaluation of any patient with suspected KD. CAA has been detected in the acute phase of illness but is more likely to develop in the subacute phase. CAA develops in about 25% of untreated children and is the leading cause of morbidity and mortality with this disease.
 - ii. The American Heart Association (AHA) classifies coronary artery changes according to z-scores.
 - (a) Less than 2 = no involvement
 - (b) 2 to less than 2.5 = dilation only
 - (c) 2.5 to less than 5 = small aneurysm
 - (d) 5 to less than 10 and absolute dimension less than 8 mm = medium aneurysm
 - (e) 10 or greater or absolute dimension of 8 mm or greater = large or giant aneurysm
 - 3. Classification according to diagnostic criteria
 - a. Classic/complete KD is defined as a fever for 5 days or more and at least four of the five principal clinical findings (note: diagnosis may be made on the fourth day of fever if at least four of the five principal clinical findings are met).
 - b. Incomplete KD is defined as a fever for 5 days or more with two or three of the principal clinical findings with supportive laboratory and/or ECHO findings per guideline algorithm.
- E. Risk of Developing CAA
- 1. Risk scoring systems for predicting CAAs are not recommended for general use (poor predictive value and not validated for all populations).
 - 2. Clinical features associated with higher risk of CAA:
 - a. Extremes of age (younger than 1 year or older than 9 years)
 - b. Male sex
 - c. Prolonged fever
 - d. Delay in diagnosis
 - e. Incomplete presentation
 - f. Persistent fever after initial treatment
 - 3. Laboratory markers associated with higher risk of CAA:
 - a. Elevated WBC
 - b. Bandemia
 - c. ESR and CRP (very high or persistently high)
 - d. High N-terminal pro-brain natriuretic peptide concentration
 - e. Low Plt
 - f. Low hemoglobin
 - g. Low albumin
 - 4. Coronary artery abnormalities revealed on initial ECHO before initiation of treatment equal a high risk of developing aneurysms (up to 81% of patients with an abnormal baseline ECHO have later developed aneurysms or a z-score of 2.5 or higher).
- F. Treatment
- 1. Initial treatment
 - a. Immune globulin
 - i. Place in therapy: First-line treatment to reduce the incidence of CAA, morbidity, and mortality. All patients thought to have KD should receive intravenous immune globulin (IVIG). Around 5% of patients will develop CAAs, despite treatment with IVIG.
-

- ii. Time to initiate: Start within the first 10 days of illness (ideally within 7 days). Late treatment (more than 10 days) should still be initiated for children who are febrile or have aneurysms and ongoing systemic inflammation (elevated ESR or CRP). Administration before the fifth day of illness does not reduce the risk of CAA but may increase the need for re-treatment.
 - iii. Single-dose IVIG of 2 g/kg usually infused over 10–12 hours is superior to 400-mg/kg infusions/day for 4 consecutive days.
 - iv. Infusion-related reactions (flushing, changes in heart rate, changes in blood pressure, fever, chills, nausea, vomiting) may respond to slowing or discontinuing the infusion. Premedication with acetaminophen and diphenhydramine is recommended. Hypersensitivity and anaphylactic reactions may occur. Other adverse effects include aseptic meningitis, acute renal failure, thromboembolic events, and autoimmune hemolytic anemia.
 - v. Monitoring: Vital signs at baseline, before and after each change in infusion rate, and baseline and post-infusion renal function, urinary output, and hemoglobin
 - vi. May interfere with the efficacy of live vaccines (measles/mumps/rubella and varicella). It is recommended to defer measles/mumps/rubella vaccination for 11 months after immune globulin. If risk of measles exposure is high, may give vaccine and re-immunize at least 11 months after immune globulin if inadequate serologic response.
- b. Aspirin
- i. Place in therapy: High-dose aspirin may shorten the duration of fever. Long-term use of low-dose aspirin as an antiplatelet is recommended.
 - ii. Dose:
 - (a) Moderate-dose therapy at 30–50 mg/kg/day to high-dose therapy at 80–100 mg/kg/day orally in four divided doses during the acute phase of illness until afebrile for 48–72 hours is recommended by the AHA. Moderate- to high-dose therapy may continue until day 14 of illness or until fever subsides.
 - (b) Low-dose therapy at 3–5 mg/kg/day orally once daily after moderate- or high-dose therapy is discontinued is recommended by the AHA. Low-dose aspirin should continue for 6–8 weeks until repeat ECHO reveals no evidence of coronary artery changes.
 - iii. Concomitant nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) may antagonize aspirin; therefore, not recommended.
 - iv. Influenza vaccine recommended to prevent Reye syndrome. Varicella vaccine may be given to prevent Reye syndrome, as known risk of wild-type infection may outweigh theoretical risk of vaccine. If varicella vaccine given, consider alternative antiplatelet for 6 weeks after vaccine.
- c. Corticosteroids
- i. Place in therapy: Initial therapy for patients at high risk of developing CAAs and second-line therapy for patients whose initial treatment regimen with immune globulin fails
 - ii. Mechanism of action: Reduction in circulating inflammatory cytokines
 - iii. Dose: Longer courses (e.g., methylprednisolone/prednisolone/prednisone 2 mg/kg/day until afebrile with tapering over 2–3 weeks) are recommended by the AHA instead of pulse doses of methylprednisolone 30 mg/kg once for initial treatment.
 - iv. Special consideration: No definitive scoring systems for determining high-risk patients have been validated for populations outside Japan. Adding corticosteroids to initial therapy with immune globulin and aspirin should be considered only for patients with coronary artery abnormalities on baseline ECHO or for patients with clinical or laboratory features that may place them at high risk of developing CAA.

2. Treatment for patients who are resistant to initial-dose IVIG
 - a. Up to 20% of patients may have persistent fever (defined as a temperature of 100.4°F [38°C] or higher that persists beyond 48 hours after starting immune globulin [i.e., at least 36 hours after completing IVIG]) or recrudescent fever (defined as a temperature of 99.5°F [37.5°C] or less for more than 24 hours after IVIG, followed by a temperature of 100.4°F [38°C] or higher).
 - b. Treatment options for patients whose initial immune globulin dose fails
 - i. IVIG: Repeat 2 g/kg dose within 2–7 days after initial IVIG infusion. 4%–8% of patients may not respond to second IVIG dose.
 - ii. Corticosteroids (either pulse dosing of methylprednisolone at 30 mg/kg/dose intravenously for 3 days or prednisolone/prednisone tapering course over 2–3 weeks)
 - iii. Infliximab:
 - (a) Common third-line agent; also has been used as a second-line agent to replace the second infusion of IVIG
 - (b) Dose: 5 mg/kg intravenous infusion over 2–3 hours
 - (c) Special considerations: Complete tuberculin skin testing before treatment. Live vaccines should not be administered concurrently.
 - iv. Etanercept
 - (a) Potential third-line agent; has been studied as a first-line agent in combination with immune globulin and aspirin
 - (b) Dose: 0.8 mg/kg/dose (maximum 50 mg) subcutaneously once weekly for three doses. If used as a first-line agent, first dose is given within 24 hours of completing immune globulin (day 0), with second and third doses given on days 7 and 14.
 - (c) Special considerations: Complete tuberculin skin testing before treatment. Live vaccines should not be administered concurrently.
 - v. Cyclosporine
 - (a) Third-line agent for patients in whom two doses of immune globulin therapy have failed
 - (b) Dose: 3 mg/kg/day intravenously divided into two doses, followed by 4–8 mg/kg/day orally divided into two doses when afebrile more than 24 hours. Doses are adjusted according to therapeutic drug monitoring. Begin tapering the dose once the patient is afebrile, is improving clinically, and has a CRP of 1 mg/dL or less or after 2 weeks of therapy, whichever is longer. Taper dose by 10% every 3 days over 1 month.
 - (c) Special considerations: Cyclosporine microemulsion liquid (Neoral) is preferred for absorption. Avoid grapefruit, pomegranate, and star fruit products, which may inhibit cyclosporine metabolism.
 - vi. Rituximab and anakinra have been used to treat resistant KD (J Pediatr 2012;160:875-6; Autoimmun Rev 2018;17:768-74; Arthritis Rheumatol 2021;73:151-61); however, no prospective clinical trials have been published to establish their routine use as third-line agents.
 3. Prevention of coronary thrombi during the acute phase of illness
 - a. Low-dose aspirin for patients without evidence of CAA for 4–6 weeks
 - b. For patients with rapidly expanding CAA or a maximum z-score of 10 or greater, aspirin plus low-molecular-weight heparin (goal anti-Xa 0.5–1 unit/mL) or warfarin (goal INR 2–3)
 - c. For patients at increased risk of thrombosis (e.g., large or giant aneurysms) and a recent history of coronary artery thrombosis, triple therapy with aspirin plus a second antiplatelet agent plus low-molecular-weight heparin (goal anti-Xa 0.5–1 unit/mL) or warfarin (goal INR 2–3)
 4. Treatment of coronary thrombi: For patients with actual or impending occlusion of the arterial lumen, thrombolytic therapy (with low-dose aspirin and low-dose heparin) or mechanical restoration of coronary artery blood flow at cardiac catheterization

Patient Cases

Questions 1 and 2 pertain to the following case.

J.L. is a 10-year-old boy (weight 33.2 kg) who presents with a history of fever for 5 days accompanied by a rash, conjunctivitis, and cherry-red lips. He continues to have a negative infectious workup. His CRP and ESR are mildly elevated. After 24 hours of remaining afebrile off antibiotics, he receives a diagnosis of a viral illness and is discharged home. Two days later, he returns because of recurrent fevers at home. Repeat CBC shows Plt 100,000/mm³. The following day, an ECHO reveals mild dilatation of the left and right coronary arteries.

1. Which is best for J.L.'s initial treatment?
 - A. Immune globulin with high-dose aspirin.
 - B. Immune globulin with medium-dose aspirin plus corticosteroids.
 - C. Corticosteroids.
 - D. Infliximab.
2. J.L. has been afebrile for 72 hours, and the team is preparing for discharge. The rheumatologist requested a repeat ECHO just prior to discharge from the hospital. This ECHO reveals an aneurysm with a z-score of 10 in the left anterior descending artery and an aneurysm with a z-score of 2.5 in the right coronary artery. Which is the best treatment for J.L. at this time?
 - A. High-dose aspirin until the aneurysm regresses.
 - B. Clopidogrel until the aneurysm regresses.
 - C. Low-dose aspirin with clopidogrel until the aneurysm regresses.
 - D. Low-molecular-weight-heparin and low-dose aspirin until the aneurysm regresses.

Questions 3–5 pertain to the following case.

E.R. is a 6-month-old girl (weight 7.4 kg) who meets the diagnostic criteria for KD and has an initial ECHO that reveals an aneurysm with a z-score of 10 in the right coronary artery.

3. Which is the most appropriate initial treatment for E.R.?
 - A. Immune globulin and medium-dose aspirin followed by corticosteroids.
 - B. Immune globulin and medium-dose aspirin followed by infliximab.
 - C. Immune globulin and medium-dose aspirin followed by cyclosporine.
 - D. Immune globulin and medium-dose aspirin followed by alteplase.
4. E.R. received treatment, but she remains febrile. Her temperature continues to be 100.5°F–101.5°F (38.1°C–38.6°C) up to 40 hours after completing her immune globulin-containing regimen. On her daily serum chemistries, her SCr has risen from 0.3 mg/dL pretreatment to 0.9 mg/dL posttreatment, and BUN has increased from 3 mg/dL to 8 mg/dL. Her urinary output has decreased from 2.5 mL/kg/hour during the previous 24 hours to 0.2 mL/kg/hour. She is maintaining good oral intake and otherwise appears well hydrated and well nourished. Which would be best for treating E.R. at this time?
 - A. Repeat immune globulin, and continue medium-dose aspirin until afebrile for 48 hours.
 - B. Repeat immune globulin, continue medium-dose aspirin until afebrile for 48 hours, and add corticosteroids.
 - C. Repeat immune globulin, continue medium-dose aspirin until afebrile for 48 hours, and add infliximab
 - D. Give infliximab, and continue medium-dose aspirin until afebrile for 48 hours.

Patient Cases (*continued*)

5. E.R. now has received a second course of therapy, has remained afebrile, has a stable cardiac examination, and is ready for discharge. Because her admission occurred in October and she has a 2-year-old brother in day care, her mother asks if E.R. should receive the influenza vaccine before discharge. Which vaccination recommendation is best for E.R.?
- A. Injectable influenza vaccine is not recommended for E.R. because it would not be effective after high-dose immune globulin.
 - B. Injectable influenza vaccine is not recommended because E.R. will be taking long-term salicylates and is at high risk of developing Reye syndrome.
 - C. Injectable influenza vaccine is recommended because E.R. is at a higher risk of developing complications related to influenza infection than of developing Reye syndrome.
 - D. Injectable influenza vaccine is recommended because E.R. will not require long-term salicylates and is not at risk of developing Reye syndrome.

II. CONGENITAL HEART DISEASES

- A. Classification of Congenital Heart Disease (CHD)
 - 1. Broadly classified into acyanotic or cyanotic lesions. Acyanotic lesions generally maintain normal or excessive blood flow to the pulmonary vasculature but limit blood flow to the systemic vasculature. Cyanotic lesions generally maintain normal blood flow to the tissues but may limit blood flow to the lungs. The result is that blood being delivered to the tissues is not highly saturated.
 - 2. Acyanotic lesions
 - a. Further subdivided into lesions that cause an increased volume load to the heart (left-to-right shunting of blood) or an increased pressure load on the heart (impeding ventricular outflow)
 - b. Atrial septal defect
 - i. Blood is shunted from left to right through an opening in the membrane separating the right and left atria, resulting in overcirculation of the lungs with highly saturated blood from the left atrium.
 - ii. Overcirculation of the lungs can cause pulmonary edema, increased pulmonary pressures, and right ventricular enlargement.
 - iii. Right-sided CHF or arrhythmia from right atrial enlargement is rare. Many patients are asymptomatic unless other heart defects are present.
 - iv. Surgical patch closure, usually at 2–4 years of age, is the primary treatment.

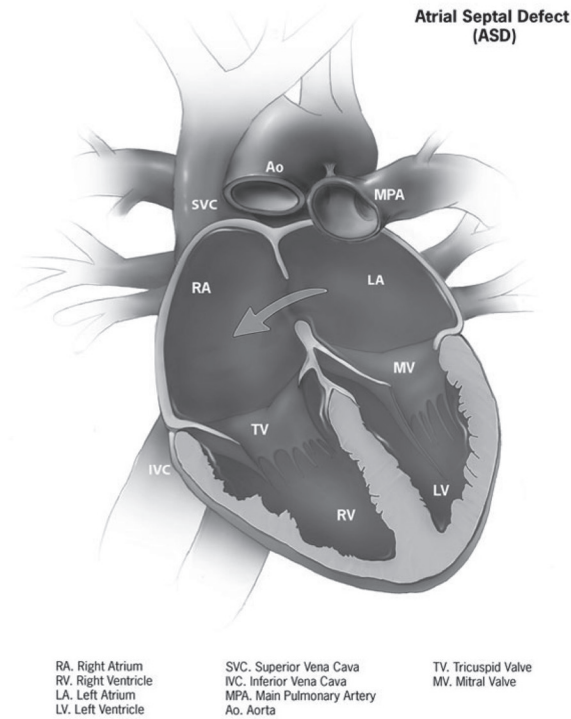


Figure 1. Atrial septal defect.

Available at www.cdc.gov/ncbddd/heartdefects/specificdefects.html.

- c. VSD
 - i. Blood is shunted from left to right through an opening in the membrane separating the right and left ventricles, resulting in overcirculation of the lungs with highly saturated blood from the left ventricle.
 - ii. Overcirculation of the lungs can cause pulmonary edema, increased pulmonary pressures, and right ventricular enlargement.
 - iii. VSD is more likely to cause significant sequelae (e.g., CHF) than is atrial septal defect.
 - iv. If the VSD is small at birth or begins to spontaneously close, surgery or pharmacologic intervention is rarely needed.
 - v. If signs and symptoms of CHF develop with a moderate to large defect, surgical patch closure will be required. Patients can be treated with medications and a calorically dense enteral formula to promote weight gain until surgery is practical.

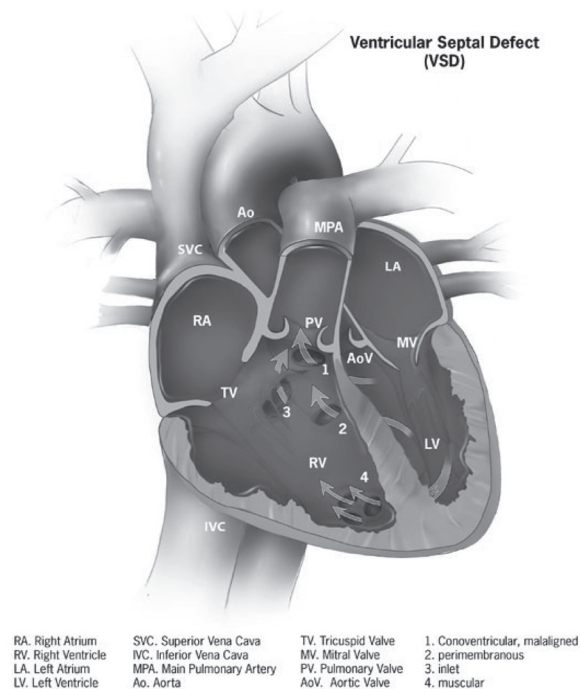


Figure 2. Ventricular septal defect.

Available at www.cdc.gov/ncbddd/heartdefects/specificdefects.html.

d. Coarctation of the aorta (CoA)

- i. CoA is a narrowing of the aorta that causes increased pressure in the left ventricle and reduced left ventricular outflow.
- ii. Coarctation usually occurs proximal to the ductus arteriosus and may in fact be related to ductal tissue encircling the aorta causing the stricture.
- iii. Ultimately, pulmonary edema and hypertension may develop, as blood leaving the lungs is impeded by high left atrial pressures. Sequelae of the stricture will depend on the degree of narrowing, location of the stricture, and patency of the ductus arteriosus.
- iv. Mild strictures are usually asymptomatic.
- v. Patients with severe narrowing or an interrupted aorta may be relatively asymptomatic shortly after birth because of the presence of a PDA. When the ductus arteriosus begins to close shortly after birth, the patient may develop life-threatening cardiogenic shock as systemic perfusion drops.
- vi. For patients who are symptomatic and dependent on the ductus arteriosus, alprostadil infusions are used to maintain patency of the ductus arteriosus as a bridge to palliative or corrective procedures. If the ductus arteriosus has already closed at the time of diagnosis and cannot be reopened, alprostadil may still be used to relax the tissue causing the stricture.
- vii. Atrial balloon septostomy is a palliative procedure.
- viii. Endovascular interventions (balloon angioplasty or stents) or surgical repair (e.g., end-to-end anastomosis) of the coarctation may lead to rebound hypertension because of stimulation of the sympathetic nervous system and renin-angiotensin-aldosterone system (RAAS). Hypertension is usually responsive to β -blockers and angiotensin-converting enzyme inhibitors (ACEIs). Hypertension in the immediate postoperative period is also responsive to intravenous nitroprusside or nitroglycerin. Patients may develop hypertension immediately after intervention, or much later (even years afterward).

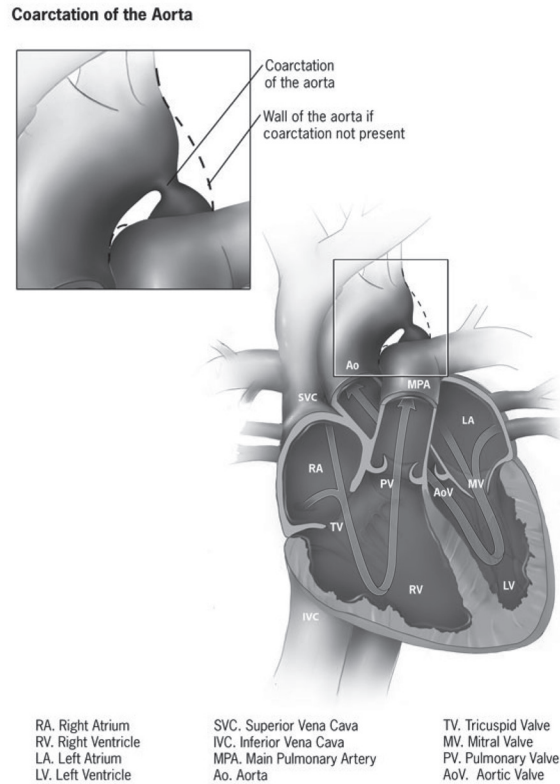


Figure 3. Coarctation of aorta.

Available at www.cdc.gov/ncbddd/heartdefects/specificdefects.html.

- e. PDA (see Neonatology chapter)
- 3. Cyanotic lesions
 - a. Cyanotic lesions may be divided into those that impede the delivery of oxygenated blood to the systemic circulation and those that impede delivery of blood to the lungs for oxygenation.
 - b. Transposition of the great arteries (TGA)
 - i. TGA is the most common cardiac cause of cyanosis presenting in the newborn period.
 - ii. With TGA, the PA is usually connected to the left ventricle (some patients may have pulmonary atresia or absent PA), and the aorta is connected to the right ventricle.
 - iii. Desaturated blood from the right ventricle is pumped to the systemic circulation, and oxygenated blood from the left ventricle is pumped to the lungs to form two parallel circulations.
 - iv. Other heart defects (e.g., atrial septal defect or VSD) or collaterals that allow oxygenated blood to reach the tissues are critical for survival.
 - v. Alprostadil can be crucial to maintain an open ductus arteriosus.

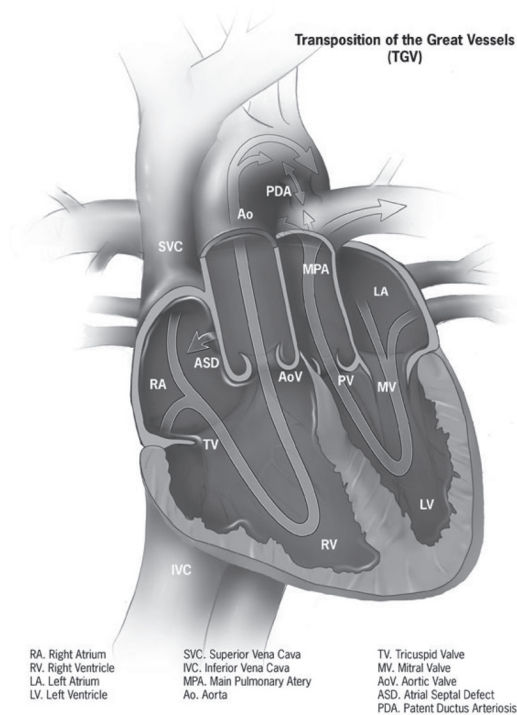


Figure 4. Transposition of the great arteries.

Available at www.cdc.gov/ncbddd/heartdefects/specificdefects.html.

- c. Tetralogy of Fallot (ToF)
 - i. ToF is the most common cause of cyanosis after 1 year of age.
 - ii. ToF is characterized by four main defects: VSD, overriding aorta (i.e., the aortic root arises from the VSD), right ventricular hypertrophy (the classic “boot-shaped” heart), and right ventricular outflow tract obstruction.
 - iii. Pulmonary blood flow depends on the severity of the right ventricular outflow tract obstruction.
 - iv. Obstruction of pulmonary blood flow may be infundibular (i.e., a muscular constriction at the area just below the pulmonic valve), valvar (e.g., valve leaflet fusion), or supravalvar (e.g., pulmonary stenosis or atresia). The degree of muscular constriction at the subpulmonic level varies; thus, the degree of cyanosis in patients with muscular obstruction varies.
 - v. Right-to-left shunting across the VSD depends on the severity of right ventricular outflow tract obstruction and systemic vascular resistance.
 - vi. Infants with mild to moderate obstruction remain relatively acyanotic but may have intermittent episodes of subpulmonic spasm known as hypercyanotic or “tet” spells. These patients may develop heart failure because of left-to-right shunting across the VSD. Infants with severe obstruction develop significant cyanosis shortly after birth. Maintaining a PDA with alprostadil is critical for survival until a surgical palliative procedure is done.
 - vii. Hypercyanotic spells usually occur more often as children get older. Spells may occur because of a physical stress (e.g., agitation from vaccinations or playing). Stress or physical exertion may cause infundibular spasm and a decrease in pulmonary blood flow. Physical exertion also increases oxygen demand in excess of supply. This leads to tachypnea and relative hypoxemia. In response, vasodilation occurs to improve oxygen delivery to the tissues. Vasodilation causes the systemic vascular resistance to drop, which leads to greater right-to-left shunting across the VSD and further worsening of pulmonary blood flow.

- viii. Management of hypercyanotic spells includes placing the child in a knee-to-chest position to increase systemic vascular resistance, providing supplemental oxygen to relieve hypoxemia (limited usefulness), and modest fluid boluses (5–10 mL/kg) to increase systemic vascular resistance. Morphine may be used to blunt tachypnea, decrease agitation, and relax the infundibular spasm. β -Blockers (propranolol and esmolol) also may be used to relax the subpulmonic tissue, prevent a decrease in systemic vascular resistance, and reduce tachypnea. Phenylephrine may be used to increase systemic vascular resistance to override the right-to-left shunting across the VSD. If these measures fail to break the hypercyanotic spell, an emergency systemic-to-PA shunt will be needed.

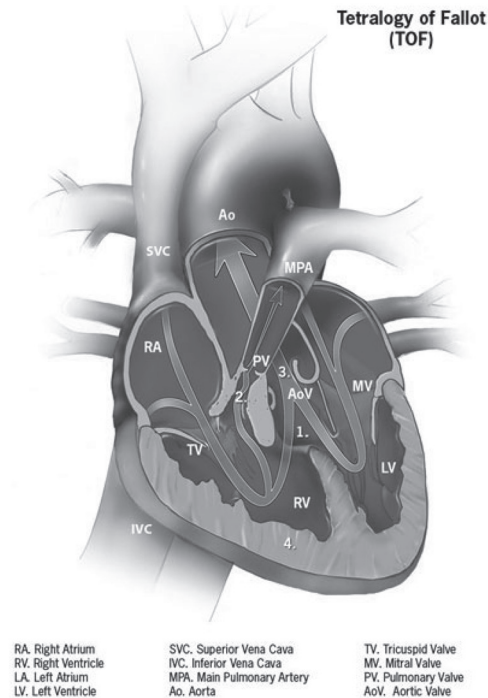


Figure 5. Tetralogy of Fallot.

Available at www.cdc.gov/ncbddd/heartdefects/specificdefects.html.

- d. Hypoplastic left heart syndrome
 - i. Hypoplastic left heart syndrome is characterized by left ventricular outflow tract obstruction. It is associated with the under-development of the left ventricle, aorta, aortic arch, and mitral atresia or stenosis. Systemic perfusion relies on right-to-left shunting from the PA to the aorta through the ductus arteriosus.
 - ii. Closure of the ductus arteriosus leads to a significant decrease in systemic perfusion, resulting in hypoxemia, acidosis, and shock. Alprostadil is critical for survival until surgical palliation.
 - iii. Treatment includes either a primary cardiac transplant or staged functionally univentricular palliative surgical procedures. Palliation involves the Norwood procedure (or Sano modification of the Norwood) or the hybrid procedure usually within 1 week of age, the bidirectional Glenn (hemi-Fontan) operation usually within 3–6 months of age, and the Fontan procedure usually at 18 months to 5 years of age.

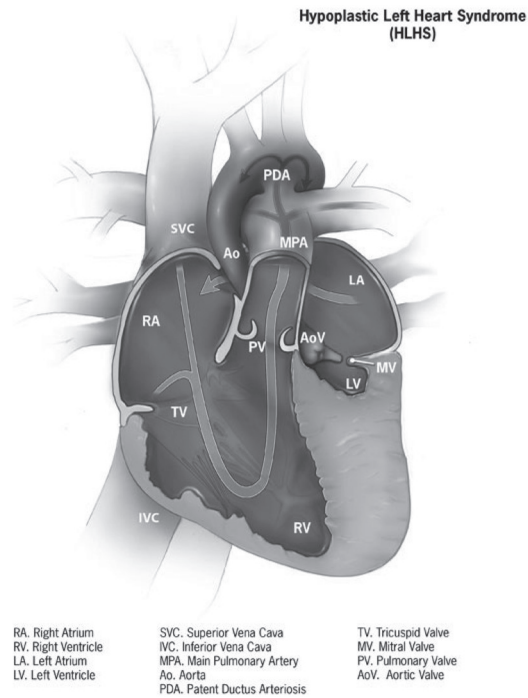


Figure 6. Hypoplastic left heart syndrome.

Available at www.cdc.gov/ncbddd/heartdefects/specificdefects.html.

B. Complications of CHD

1. Major complications include:
 - a. CHF
 - b. Arrhythmias (reviewed in section IV)
 - c. Thromboembolic disorders (reviewed in section V)
 - d. PHN (reviewed in section VI)
 - e. Infective endocarditis
2. Except for PDA, pharmacologic therapy manages symptoms associated with complications that develop before or after palliative or corrective surgery.

C. Pharmacologic Management

1. Closure of the ductus arteriosus (see Neonatology chapter)
2. Maintenance of an open ductus arteriosus: Management of ductal-dependent lesions (e.g., CoA, TGA, ToF, and hypoplastic left heart syndrome). Alprostadil also may relax a CoA because some strictures are formed by bands of ductal tissue.
 - a. Alprostadil dose: 0.05–1 mcg/kg/min; rapid onset and offset of action due to short half-life (ductus begins to close within 1–2 hours after infusion discontinued)
 - b. Adverse effects: Hypotension, bradycardia, arrhythmias, fever, apnea, necrotizing enterocolitis, renal dysfunction, thrombocytopenia
3. Rebound/late hypertension after CoA repair: ACEIs, angiotensin receptor blockers (ARBs), and β -blockers preferred; alternatives include nitroprusside, nitroglycerin, and nicardipine infusions.

Table 1. Pharmacologic Agents to Manage Rebound Hypertension After CoA Repair

Drug	Adverse Effects	Monitoring	Special Considerations
ACEI	• Angioedema • Anaphylactoid reactions • Cough • Hypotension • Hyperkalemia • Neutropenia • Renal dysfunction • Fever	• Blood pressure • Serum electrolytes • Renal function • WBC	• Use lower starting doses in preterm infants (risk of poor renal and cerebral blood flow) • Dose adjust for renal function (not recommended in neonates with CrCl < 30 mL/min/1.73 m²) • Contraindicated in renal artery stenosis • Enalapril/lisinopril may be preferred to captopril because of longer duration of action and once-daily dosing • Captopril may be preferred in patients < 6 mo because of less risk of hyperkalemia
ARB	• Angioedema (rare) • Hypersensitivity • Cough (rare) • Hypotension (especially first dose) • Hyperkalemia • Hypoglycemia • Anemia • Renal dysfunction	• Blood pressure • Serum electrolytes • Renal function	• Less likely to cause angioedema and cough than ACEIs • Not recommended for children < 6 yr or in children with CrCl < 30 mL/min/1.73 m² • Contraindicated in renal artery stenosis • Reduce starting dose with hepatic dysfunction (no specific dosing recommendations)
β-blockers	• Hypotension • Bradycardia • Worsening heart failure • Hypoglycemia • Hypersensitivity reactions • Serious cutaneous reactions (including Stevens-Johnson syndrome) (propranolol) • Depression (propranolol)	• Blood pressure • Heart rate • ECG	• Do not abruptly discontinue therapy; taper over 2 wk • Withdrawal effects may occur when discontinued (esmolol) • Use with caution in patients with bronchospastic disease (e.g., nonallergic bronchospasm or chronic bronchitis) • Use with caution in patients with peripheral vascular disease (e.g., Raynaud) • Use with caution in WPW • Avoid with severe bradycardia, AV block, sick sinus syndrome • May mask signs of hypoglycemia • Dose adjust for renal function (atenolol)

Table 1. Pharmacologic Agents to Manage Rebound Hypertension After CoA Repair (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Nitroprusside	• Hypotension • Cyanide toxicity • Thiocyanate toxicity	• Blood pressure • Heart rate • Respiratory rate • Acid-base status • Mental status • Renal function • Hepatic function • Cyanide concentrations if hepatic dysfunction • Thiocyanate concentrations if renal dysfunction • Methemoglobin levels	• May be used in the immediate postoperative period • Doses ≥ 1.8 mcg/kg/min associated with increased cyanide concentrations • Limit to duration < 3 days, and avoid doses ≥ 4 mcg/kg/min • Cyanide and/or thiocyanate toxicity with hepatic and/or renal dysfunction • Tachycardia, tachypnea, vomiting, metabolic acidosis, and mental status changes are symptoms of toxicity • Thiosulfate or hydroxycobalamin may limit toxicity
Nitroglycerin	• Hypotension • Bradycardia • Headache	• Blood pressure • Heart rate	• May be used in the immediate postoperative period • Not used routinely for acute decompensated heart failure • Prepare in nonpolyvinyl chloride or glass containers and administer with nonpolyvinyl chloride administration sets
Nicardipine	• Hypotension • Tachycardia • Edema • Flushing • Headache	• Blood pressure • Heart rate • Hepatic function • Renal function	• Dose adjust for renal or hepatic dysfunction (no specific manufacturer recommendations) • May worsen heart failure because of negative inotropic effects • Beware drug-drug interactions (weak inhibitor of CYP2D6; minor substrate of CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4, and P-glycoprotein) • Some products may contain propylene glycol

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AV = atrioventricular; CrCl = creatinine clearance; ECG = electrocardiogram; WBC = white blood cell; WPW = Wolff-Parkinson-White (syndrome).

4. CHF

- a. Signs and symptoms of CHF may develop before or after palliative/corrective surgery for CHD. About 90% of all CHF cases in children occur before the first year of life and are caused by CHD.

Box 1. Common Signs and Symptoms of Congestive Heart Failure

Impaired cardiac output
• Tachycardia • Cardiomegaly • Diaphoresis • Failure-to-thrive
Pulmonary venous congestion (left sided)
• Tachypnea and labored breathing • Orthopnea (older children) • Poor feeding • Wheezing and crackles
Systemic venous congestion (right sided)
• Hepatomegaly • Edema (puffy eyelids, hands, and feet)

- b. Heart failure associated with obstructive lesions (e.g., CoA) and ductal-dependent lesions (e.g., hypoplastic left heart syndrome or TGA with intact ventricular septum) usually appear in the first week of life.
- c. Heart failure related to volume overload with left-to-right shunt lesions (e.g., VSD or PDA) usually appears when pulmonary vascular resistance drops at 4–6 weeks of life. An isolated atrial septal defect generally does not cause CHF unless it remains uncorrected into adulthood.
- d. Heart failure presenting after the first year in patients with CHD is most likely related to palliative surgery (e.g., Fontan procedure for hypoplastic left heart syndrome or atrial switch for TGA) or infective endocarditis.
- e. In general, management of heart failure is directed toward reducing cardiac preload, increasing inotropy, reducing afterload, and preventing cardiac remodeling (myocardial hypertrophy, interstitial fibrosis, apoptosis of myocytes).
- f. Common agents used post-cardiac surgery and in the setting of acute decompensated heart failure include diuretics, inotropes, inodilators, and vasodilators.

Table 2. Activity of Agents Used to Manage Heart Failure

Agent(s)	Preload	Chronotropy	Inotropy	Afterload	Pulmonary Vascular Resistance	Cardiac Remodeling
Aldosterone antagonists	↓	↔	↔	↔	↔	Slows
ARBs	↔	↔	↔	↓	↔	Slows
ACEIs	↔	↔	↔	↓	↔	Slows
β-blockers	↔	↓	↔	↓	↓	Reverses
Digoxin	↔	↓	↑	↔	↔	↔
Diuretics	↓	↔	↔	↔	↔	↔
Dobutamine	↔	↑	↑	↓ (modest)	↔	↔
Epinephrine	↔	↑	↑	↓ (low doses)	↔	↔
Ivabradine	↔	↓	↔	↔	↔	↔
Milrinone	↔	↔	↑	↓	↓	↔
Nitroprusside	↓	↔	↔	↓	↓	↔
Nitroglycerin	↓	↔	↔	↓ (modest)	↓	↔
Sacubitril-valsartan	↓	↔	↔	↓	↓	Reverses

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

- g. Common agents used for chronic heart failure include diuretics, aldosterone antagonists, ACEIs, ARBs, digoxin, and β-blockers, as well as the newer agents ivabradine and sacubitril-valsartan.
 - i. Ivabradine
 - (a) Reduces heart rate by targeting the inward funny current (I_f) in sinoatrial tissue.
 - (b) FDA approved (greater than or equal to 6 months of age) for treatment of stable symptomatic heart failure caused by dilated cardiomyopathy in children who are in sinus rhythm with an elevated heart rate and ejection fraction below 45% (J Am Coll Cardiol 2017;70:1262-72). Study targeted greater than or equal to a 20% reduction in resting heart rate from baseline without bradycardia or symptoms. Approval in adult patients based on ejection fraction below 35% with persistent tachycardia despite optimal β-blocker or intolerance to β-blockers.
 - ii. Sacubitril-valsartan
 - (a) Effects natriuresis and vasodilation, and reverses cardiac remodeling through dual action of neprilysin inhibition (sacubitril) and renin-angiotensin-aldosterone system blockade (valsartan).
 - (b) FDA approved (greater than or equal to 1 year of age) for treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction according to preliminary results of the PANORAMA-HF study (Am Heart J 2017;193:23-34).
5. Hypercyanotic spells
 - a. Morphine 0.1 mg/kg subcutaneously, intramuscularly, intravenously
 - b. Propranolol to treat hypercyanotic spells: 0.15–0.25 mg/kg/dose intravenously (maximum initial dose 1 mg); may repeat dose once. To prevent hypercyanotic spells until palliative or corrective surgery: 0.5–1 mg/kg/dose orally every 6 hours (usual dose 1–2 mg/kg/dose orally every 6 hours). Beware dosing errors due to significant difference between intravenous and oral doses.
 - c. Esmolol 500-mcg/kg intravenous loading dose, followed by 50- to 100-mcg/kg/minute intravenous infusion

- d. Phenylephrine
 - i. Mechanism of action: Increases systemic vascular resistance (afterload) by stimulating α_1 -adrenergic receptors
 - ii. Dose: 5–20 mcg/kg intravenously every 15 minutes as needed, followed by 0.1–5 mcg/kg/minute intravenous infusion if prolonged therapy is required
 - iii. Adverse effects: Severe hypertension, renal dysfunction, metabolic acidosis, sloughing of skin/necrosis of the extremities
 - iv. Monitoring values: Blood pressure, heart rate, central venous pressure, peripheral perfusion (capillary refill)
 - v. Special considerations: Risk of severe peripheral vasoconstriction, so reserve for patients who do not respond to measures that are more benign
- 6. Prevention of infective endocarditis
 - a. Patients with certain types of CHD may be at risk of developing infective endocarditis after procedures that cause bacteremia (e.g., dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth or perforation of the oral mucosa). These patients should receive antibacterial prophylaxis before the procedure.
 - b. Not all dental procedures require prophylaxis (e.g., typical orthodontic or prosthodontic procedures or radiographs of teeth). Shedding of deciduous teeth and bleeding secondary to trauma to the lips or oral mucosa do not require antibiotic prophylaxis.
 - c. Patients at risk:
 - i. Mechanical or prosthetic valve
 - ii. Cyanotic lesions not fully repaired (including those with surgical shunts or conduits)
 - iii. Heart defect completely repaired with a prosthetic material or device within the first 6 months after repair (i.e., endothelialization of prosthesis occurs within 6 months after procedure)
 - iv. Repaired heart defect that has residual defects (e.g., persistent leaks or abnormal flow around a prosthetic patch or device)
 - v. Previous infective endocarditis
 - d. A one-time antibiotic dose should be administered 30–60 minutes before the procedure.
 - i. Oral therapy in patients not allergic to penicillins:
 - (a) Children: Amoxicillin 50 mg/kg/dose (not to exceed adult dose)
 - (b) Adults: Amoxicillin 2 g/dose
 - ii. Unable to take oral antibiotics and not allergic to penicillins:
 - (a) Children: Ampicillin, cefazolin, or ceftriaxone 50 mg/kg/dose (not to exceed adult dose) intramuscularly or intravenously
 - (b) Adults: Ampicillin 2 g/dose or cefazolin/ceftriaxone 1 g/dose intramuscularly or intravenously
 - iii. Oral therapy if allergic to penicillins:
 - (a) Children: Cephalexin 50 mg/kg/dose* or clindamycin 20 mg/kg/dose or azithromycin/clarithromycin 15 mg/kg/dose (not to exceed adult dose)
 - (b) Adults: Cephalexin 2 g/dose* or clindamycin 600 mg/dose or azithromycin/clarithromycin 500 mg/dose
 - iv. Unable to take oral antibiotics and allergic to penicillins:
 - (a) Children: Cefazolin/ceftriaxone 50 mg/kg/dose or clindamycin 20 mg/kg/dose (not to exceed adult dose) intramuscularly or intravenously
 - (b) Adults: Cefazolin/ceftriaxone 1 g/dose or clindamycin 600 mg/dose intramuscularly or intravenously
 - v. Do not select cephalosporins in penicillin-allergic patients with a history of anaphylaxis, angioedema, or urticaria (consider clindamycin or azithromycin/clarithromycin).

*Another first- or second-generation oral cephalosporin in equivalent dosages may be substituted for cephalexin.

Patient Cases

6. B.P. is a 4-week-old term girl (weight 4.2 kg) who was given a diagnosis of moderate CoA. She underwent an aortic balloon dilatation procedure in the cardiac catheterization laboratory. She experienced some elevated blood pressures in the intensive care unit that responded to nitroprusside infusion. Later in the week, she was transferred to the intermediate medical unit where her blood pressures began to upwardly trend (SBPs 110–115 mm Hg). Which is best to manage B.P.'s blood pressure at this time?
- A. Captopril.
 - B. Milrinone.
 - C. Esmolol.
 - D. Nitroglycerin.

Questions 7 and 8 pertain to the following case.

7. E.P. is a 13-month-old girl (weight 9.2 kg) who was given a diagnosis shortly after birth of ToF without PA stenosis or pulmonary valvular disease and only a mild reduction in pulmonary blood flow. She has maintained good oxygen saturations, growth, and development. She went to the primary care physician's office today to receive her 12-month vaccinations. According to her mother, E.P. was quite upset at the office and began having a temper tantrum. After her vaccinations, she was crying inconsolably. Her lips turned blue, and she had difficulty breathing. Emergency services were called, and she was transported to the ED. On arrival, her respiratory rate is 42 breaths/minute and oxygen saturations are 75%. Which intervention is most appropriate for initial treatment of E.P.?
- A. Knee-to-chest positioning, supplemental oxygen, and morphine.
 - B. Knee-to-chest positioning, supplemental oxygen, and phenylephrine.
 - C. Knee-to-chest positioning, propranolol, and phenylephrine.
 - D. Knee-to-chest positioning, morphine, and phenylephrine.
8. It is now 1 year since E.P. had a palliative systemic-pulmonary shunt placed to manage her ToF until surgical correction. Although her mother has scheduled an appointment with a dentist for E.P.'s first teeth cleaning, she is considering canceling the appointment because of her concerns about endocarditis. Which would be the best recommendation for E.P.'s mother?
- A. Avoiding dental cleanings because E.P. is at high risk of bacterial endocarditis.
 - B. Dental cleaning because E.P. is not at risk of bacterial endocarditis.
 - C. Dental cleaning with amoxicillin prophylaxis.
 - D. Dental cleaning with ciprofloxacin prophylaxis.

III. PEDIATRIC HYPERTENSION

- A. Epidemiology
 - 1. Concurrent conditions associated with hypertension in children and adolescents:
 - a. CHD
 - b. Renal disease
 - c. Urologic disease
 - d. Systemic illnesses associated with hypertension
 - e. Medications known to cause hypertension
 - f. Malignancy

- g. Transplantation
 - h. Obesity
 - i. History of prematurity
 - j. Sleep disordered breathing
2. Concurrent conditions associated with hypertension in neonates:
 - a. Umbilical artery catheter–associated thromboembolism affecting the aorta or renal arteries
 - b. Congenital renal abnormalities
 - c. Postnatal acute renal failure
 - d. Chronic lung disease (especially if long-term theophylline preparations, diuretics, and/or corticosteroids needed)
 - e. PDA
 - f. CoA
 - g. Antenatal steroids
 - h. Maternal hypertension
- B. Blood Pressure Measurements
1. Auscultation is preferred (must use an appropriately sized cuff). Blood pressures obtained by oscillometric devices that are above the 90th percentile should be repeated by auscultation.
 2. Measure in the right arm in repeated measures for consistency, for comparison with values on standard tables, and because of the possibility of CoA (falsely low readings in the left arm).
 3. Average of several blood pressure measurements taken over weeks to months is more precise in characterizing a patient's true blood pressure.
 4. Intra-arterial blood pressure measurement is the gold standard for neonates because auscultation is not practical in the neonatal ICU. Measurement by oscillometric devices may be acceptable.
- C. Blood Pressures for Age/Height/Sex
1. Standard curves denoting the 50th, 75th, 90th, and 95th percentiles for SBP and DBP in patients 0–12 months of age have been published according to the Task Force on Blood Pressure Control in Children (Pediatrics 1987;79:1-25).
 2. Standard tables listing the 50th, 90th, 95th, and 95th plus 12 mm Hg percentiles for SBP and DBP in patients 1–17 years of age have been published according to the Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents (Pediatrics 2017;140:e20171904).
 3. Data for preterm and term infants are variable. Nationally recognized standard reference tables do not exist in this population; however, a table was published of derived SBP and DBP percentiles, as well as mean arterial pressure percentiles, according to postconceptional age for infants born prematurely (Pediatr Nephrol 2012;27:17-32).
- D. Classification of Hypertension
1. All SBP and DBP percentiles are established according to age, height, and sex. SBP and DBP should be measured on at least three separate occasions and averaged to determine blood pressure classification. If SBP and DBP classifications differ, use the higher value.
 2. Normal blood pressure: Less than 90th percentile (age 1-13 years); less than 120/80 mm Hg (age greater than or equal to 13 years)
 3. Elevated blood pressure: 90th to less than 95th percentile or 120/80 mm Hg to less than 95th percentile (whichever is lower) for ages 1-13 years; 120-129/<80 mm Hg for ages greater than or equal to 13 years
 4. Stage 1 hypertension: 95th to less than 95th percentile plus 12 mm Hg or 130-139/80-89 mm Hg (whichever is lower) for ages 1-13 years; 130-139/80-89 mm Hg for ages greater than or equal to 13 years
 5. Stage 2 hypertension: 95th percentile plus 12 mm Hg or greater than or equal to 140/90 mm Hg (whichever is lower) for ages 1-13 years; greater than or equal to 140/90 mm Hg for ages greater than or equal to 13 years

6. Severe hypertension: SBP or DBP well above stage 2 hypertension with symptoms. Hypertensive emergencies are associated with encephalopathy and seizures. Hypertensive urgencies are usually associated with less serious symptoms (e.g., vomiting and severe headache).
 7. White-coat hypertension: Blood pressure above the 95th percentile for age, height, and sex in a physician's office or clinic only (i.e., normal blood pressure in outside setting)
 8. Neonatal hypertension is less well defined, but it has been suggested that preterm neonates with blood pressure values persistently at or above the 99th percentile according to postconceptual age should have a further workup for hypertension with possible initiation of antihypertensives.
- E. Clinical Evaluation and Management of Hypertension
1. Goal blood pressure is less than 90th percentile and less than 130/80 mm Hg in adolescents greater than or equal to 13 years old, whichever is lower.
 2. For patients with chronic kidney disease and hypertension, goal blood pressure is 24-hour MAP less than 50th percentile by ambulatory blood pressure monitoring. Ambulatory blood pressure monitoring should occur at least yearly.
 3. For patients with type 1 or type 2 diabetes mellitus and hypertension, blood pressure should be monitored at each medical encounter and treated if greater than or equal to 95th percentile or greater than 130/80 mm Hg in adolescents greater than or equal to 13 years old.
 4. Lifestyle modifications include Dietary Approaches to Stop Hypertension (DASH) diet, exercise, weight loss for overweight or obese children and adolescents, and stress reduction.
- F. Principles of Antihypertensive Therapy for Chronic Hypertension
1. Initiate pharmacologic therapy for children and adolescents who:
 - a. Remain hypertensive despite lifestyle modifications
 - b. Have symptomatic hypertension
 - c. Have stage 2 hypertension without a modifiable risk factor
 - d. Have hypertension related to diabetes
 - e. Have hypertension related to chronic kidney disease
 2. Initial pharmacologic therapy should begin with a single agent.
 3. The lowest dose in the dosing range should be used at the beginning of therapy, with gradual titration to goal blood pressure (adjust every 2 weeks unless the patient is symptomatic). If the maximum dose does not achieve adequate blood pressure control or if the patient has adverse effects, a second agent from another antihypertensive class should be added. Combinations should have complimentary actions.
 4. Initial agents of choice include: ACEIs, ARBs, long-acting CCBs, or thiazide diuretics. Agents affecting the RAAS may produce a greater reduction in blood pressure than other agents. A recent head-to-head comparison of initial therapy with ACEIs or ARBs in both children and adults did not show a difference in cardiovascular endpoints, but did show a reduced incidence of adverse effects with ARBs (Hypertension 2021;78:591-603).
 5. ACEIs or ARBs are recommended for chronic kidney disease, proteinuria, or diabetes mellitus.
 6. β -blockers are not recommended as initial treatment because of adverse effects and lack of association with improved outcomes in adults.
 7. Step-down therapy may be considered for patients with sustained blood pressure control over an extended period.
 8. For hypertension in preterm neonates, the decision to treat and the antihypertensive agent to use are based on expert opinion. The recommendation is to consider drug therapy when the neonate's blood pressure is consistently at or above the 99th percentile for postconceptual age. Full-term and older infants should follow guidelines according to the Task Force on Blood Pressure Control in Children.

G. Antihypertensive Agents for Chronic Hypertension

1. Dosing tables for antihypertensive medications in children and adolescents are available in the Clinical Practice Guideline (Pediatrics 2017;140:e20171904).
2. Dosing recommendations for antihypertensive medications in infants have been published previously (Pediatr Nephrol 2012;27:17-32).

H. Principles of Antihypertensive Therapy for Hypertensive Emergency/Urgency

1. Severe hypertension is a potentially life-threatening event. Prognosis depends on the rate of rise in blood pressure, the absolute level of blood pressure, and target end-organ damage. Organs most likely to be damaged are the CNS, the eyes, the heart, and the kidneys.
2. Severe hypertension is divided into hypertensive emergency and hypertensive urgency. Hypertensive emergency has more severe end-organ damage than hypertensive urgency. Hypertensive emergency necessitates management in an ICU and usually requires intravenous antihypertensives with invasive blood pressure monitoring. Hypertensive urgency may be managed on the pediatric intermediate care unit and often with enteral antihypertensives.
3. Blood pressure should be decreased by 25% of the planned reduction in the first 8 hours, and the remainder of the planned reduction should occur over the next 12 to 24 hours. A gradual reduction is necessary to preserve cerebral autoregulation. The ultimate short-term goal is blood pressure around the 95th percentile.

I. Antihypertensive Agents for Hypertensive Emergencies

1. Some authors prefer nitroprusside, nicardipine, and esmolol intravenous infusions as first-, second-, and third-line choices for the management of hypertensive emergencies. Other authors suggest labetalol, nitroprusside, and nicardipine intravenous infusions as preferred agents.
2. If intravenous infusions are not an option, intravenous bolus or intramuscular administration of hydralazine or intravenous labetalol may be considered.
3. If intravenous administration is likely to be delayed, antihypertensive therapy may be initiated with oral immediate-release nifedipine or oral isradipine.
4. When goal blood pressure is achieved, oral antihypertensives should replace intravenous agents. Oral agents should be initiated within 6–12 hours of intravenous therapy. Intravenous medications are gradually withdrawn during the next 12–48 hours.

Table 3. Pharmacologic Agents for Hypertensive Emergency

Drug	Adverse Effects	Monitoring	Special Considerations
Enalaprilat	• Angioedema • Anaphylactoid reactions • Cough • Hypotension • Hyperkalemia • Neutropenia • Renal dysfunction	• Blood pressure • Serum electrolytes • Renal function • WBC	• Not recommended for neonates because of risk of significant, prolonged hypotension and acute renal failure • Dose adjust for renal function (not recommended in neonates with CrCl < 30 mL/min/1.73 m²) • Contraindicated in renal artery stenosis
Esmolol	• Hypotension • Bradycardia • Worsening heart failure • Hypoglycemia	• Blood pressure • Heart rate • ECG	• Ultra-short-acting and cardioselective β_1-adrenergic blocker; useful for intraoperative severe hypertension • Contraindicated in amphetamine-induced hypertension; crisis worsened with unopposed action on α-adrenergic receptors

Table 3. Pharmacologic Agents for Hypertensive Emergency (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Fenoldopam	- Tachycardia (dose related) - Hypokalemia	- Heart rate - Blood pressure - Serum electrolytes - Renal function	- Good choice for acute renal failure because of agonism of dopamine D₁ receptors and enhanced renal perfusion - Some products may contain propylene glycol
Hydralazine	- SLE-like syndrome - Peripheral neuritis - Hypotension - Flushing - Tachycardia	- Blood pressure - Heart rate - ANA	- Contraindicated in coronary artery disease - Beware drug-drug interactions - Use with caution in advanced renal dysfunction
Labetalol	- Hypotension - Bradycardia - Worsening heart failure - Hypoglycemia	- Blood pressure - Heart rate - ECG	- Heart failure may worsen, usually in first 48 hr after starting or when dose is titrated - Use with caution in WPW - Avoid with severe bradycardia, AV block, sick sinus syndrome - May mask signs of hypoglycemia
Nicardipine	- Hypotension - Tachycardia - Edema - Flushing - Headache	- Blood pressure - Heart rate - Hepatic function - Renal function	- Adjust dose for renal or hepatic dysfunction - May worsen heart failure because of negative inotropic effects - Beware drug-drug interactions (weak inhibitor of CYP2D6; minor substrate of CYP1A2, CYP2C8, CYP2C9, CYP2D6, CYP2E1, CYP3A4, and P-glycoprotein) - Some products may contain propylene glycol
Nitroprusside	- Hypotension - Cyanide toxicity - Thiocyanate toxicity	- Blood pressure - Heart rate - Respiratory rate - Acid-base status - Mental status - Renal function - Hepatic function - Cyanide concentrations if hepatic dysfunction - Thiocyanate concentrations if renal dysfunction	- Initial choice for short-term use in vasoconstricted heart failure with elevated blood pressure - Doses ≥ 1.8 mcg/kg/min associated with increased cyanide concentrations - Limit to < 3 days' duration, and avoid doses ≥ 4 mcg/kg/min - Cyanide and/or thiocyanate toxicity with hepatic and/or renal dysfunction - Tachycardia, tachypnea, vomiting, metabolic acidosis, and mental status changes are symptoms of toxicity - Thiosulfate or hydroxycobalamin may limit toxicity
Phentolamine	- Hypotension - Bradycardia - Myocardial infarction	- Blood pressure - Heart rate	- Avoid use in coronary artery disease - Useful for cocaine toxicity caused by nonselective α-adrenergic blockade (hypertension from inhibition of norepinephrine uptake) - Useful for amphetamine toxicity (hypertension from sympathomimetic and serotonergic actions) - Useful for sympathetic crisis or catecholamine toxicity (exogenous or endogenous [e.g., pheochromocytoma])

ANA = antinuclear antibody; AV = atrioventricular; CrCl = creatinine clearance; ECG = electrocardiogram; SLE = systemic lupus erythematosus; WBC = white blood cell; WPW = Wolff-Parkinson-White (syndrome).

- J. Antihypertensive Agents for Hypertensive Urgencies: Oral antihypertensives are appropriate when symptoms are not severe (e.g., neurologic sequelae).

Table 4. Pharmacologic Agents for Hypertensive Urgency

Drug	Adverse Effects	Monitoring	Special Considerations
Clonidine	• Bradycardia • Hypotension • Xerostomia • CNS depression (sedation)	• Blood pressure • Heart rate	• Useful in hemodialysis patients because of prolonged half-life with renal impairment • Avoid in cardiovascular and cerebrovascular disease • Beware use with other sedating drugs
Hydralazine	• SLE-like syndrome • Peripheral neuritis • Hypotension • Flushing • Tachycardia	• Blood pressure • Heart rate • ANA	• Contraindicated in coronary artery disease • Beware drug-drug interactions • Reduce frequency for CrCl < 50 mL/min/1.73 m²
Isradipine	• Hypotension • Syncope • Reflex tachycardia • Flushing • Dizziness • Headache	• Blood pressure • Heart rate	• Avoid in heart failure and aortic stenosis • Avoid in hypertrophic cardiomyopathy with left outflow tract obstruction • Beware use in hepatic dysfunction; may require lower dose • Substrate of CYP3A4 (major) • Beware drug-drug interactions
Minoxidil	• Fluid retention • Tachycardia • Hypotension • Syncope • Pericarditis • Pericardial effusion	• Blood pressure • Heart rate • Fluid balance	• Contraindicated in pheochromocytoma • Often used with diuretic to counteract sodium and fluid retention • Use with caution in heart failure • Use with caution with renal dysfunction
Nifedipine	• Hypotension • Headache • Nausea • Vomiting • Flushing • Tachycardia • Dizziness	• Blood pressure • Heart rate	• Avoid in heart failure • Do not crush, chew, or divide extended-release products • Substrate of CYP3A4 (major), CYP2D6 (minor) • Beware drug-drug and food-drug interactions

ANA = antinuclear antibody; CNS = central nervous system; CrCl = creatinine clearance; SLE = systemic lupus erythematosus.

Patient Cases

9. L.D. is a 17-year-old male adolescent brought to the ED by ambulance after his friends found him on the floor shaking and sweating during a “rave” party. He was extremely agitated, shaking, grinding his teeth, and yelling at people who were not in the room. Vital signs were temperature 104°F (40°C), heart rate 140 beats/minute, respiratory rate 35 breaths/minute, and blood pressure 160/100 mm Hg. After initial stabilization, he was placed under a cooling blanket and given intravenous lorazepam 4 mg. Blood pressure remained on average 155/95 mm Hg, with heart rate 128 beats/minute. Which agent would be best for initial management of L.D.’s blood pressure?
- A. Nitroprusside.
 - B. Esmolol.
 - C. Phentolamine.
 - D. Enalapril.

Questions 10–12 pertain to the following case.

K.H. is a 12-year-old girl (height 59 inches [150 cm] [25th percentile], weight 42 kg [50th percentile]) with end-stage renal disease secondary to renal dysplasia who is maintained on peritoneal dialysis. She has a history of left ventricular hypertrophy, left ventricular dysfunction (ejection fraction 36%), and hypertension. She had vomiting at home after a dialysis session with a heart rate of 120–130 beats/minute and blood pressures of 122/89 mm Hg and 134/84 mm Hg. She was brought to the ED. Her oxygen saturation was 85% on room air, and she was tachypneic with crackles and tachycardic; her blood pressure was 190/120 mm Hg. Chest radiograph revealed massive cardiomegaly and pulmonary edema. An ECHO revealed an ejection fraction of 29%, so she was transferred to the ICU to start a more urgent peritoneal dialysis regimen to control volume overload.

Blood Pressure Values for Girls by Age and Height Percentile			
Age (yr)	Blood Pressure (percentile)	Systolic Blood Pressure for 25th Percentile of Height (mm Hg)	Diastolic Blood Pressure for 25th Percentile of Height (mm Hg)
12	50th	104	61
	90th	116	75
	95th	120	78
	95th + 12 mm Hg	132	90

Data from: Flynn JT, Kaelber DC, Baker-Smith CM, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* 2017;140:e20171904.

10. Which antihypertensive agent is best for K.H. at this time?
- A. Enalaprilat.
 - B. Nicardipine.
 - C. Esmolol.
 - D. Labetalol.

Patient Cases (*continued*)

11. One month later, K.H. is discharged from the hospital on enalapril 1.5 mg twice daily. You see her in the clinic 2 weeks later. Her average blood pressures at home have been 110/65–118/70 mm Hg, and her blood pressures in the clinic are 102/60 mm Hg, 104/61 mm Hg, and 103/61 mm Hg. She has been doing well overall but has developed a dry, nonproductive cough. She has no other symptoms suggestive of a viral or bacterial illness. On physical examination, her lungs sound clear. A chest radiograph is ordered, which reveals mild but stable cardiomegaly without pulmonary edema. Which would be best for adjusting K.H.'s therapy?
 - A. Continue current enalapril dose because blood pressures are within goal range.
 - B. Increase enalapril dose because blood pressures are above goal range.
 - C. Discontinue enalapril and initiate losartan because cough is probably an adverse effect of enalapril.
 - D. Add furosemide because cough is probably the result of pulmonary congestion from heart failure.
12. It is 1 month later, and K.H.'s blood pressure readings are 125/85–128/89 mm Hg at home. Her current average blood pressure in the clinic is 130/89 mm Hg. Which would be the best treatment for K.H.?
 - A. Increase the dose of her current antihypertensive.
 - B. Counsel her to reduce her salt intake, and continue her current dose of antihypertensive.
 - C. Reduce the dose of her current antihypertensive, and add a second antihypertensive.
 - D. Increase the dose of her current antihypertensive, and add a second antihypertensive.

IV. ARRHYTHMIAS

- A. Epidemiology – The most common arrhythmias in children are sinus tachycardia (50%), supraventricular tachycardia (SVT) (13%), bradycardia (6%), and atrial fibrillation (Afib) (4.6%).
- B. Tachyarrhythmias
 1. Tachyarrhythmias are divided into three main categories: supraventricular (from above the atrioventricular [AV] node), from the AV node, and from the ventricle.
 2. SVT is the most common. Ventricular tachycardias (VTs) are the most dangerous in general because they are usually associated with hemodynamic compromise.
 3. Sinus tachycardia
 - a. Signs/symptoms: Heart rate above 140 beats/minute in children (but usually lower than 180 beats/minute); above 160 beats/minute in infants (but usually lower than 220 beats/minute)
 - b. ECG: Narrow QRS axis (0.09 second or less) with a P wave preceding each QRS complex
 - c. Etiology: Dehydration, hypovolemia, fever
 - d. Treat underlying disorder.
 4. SVT
 - a. Signs/symptoms: Infants have a heart rate above 220 beats/minute, whereas older children have a heart rate above 180 beats/minute. Infants may present with fussiness, lethargy, poor feeding, sweating with feeding, or pallor. Older children may describe palpitations, chest pain, dizziness, or shortness of breath. SVT is the most common arrhythmia associated with chest pain.
 - b. ECG: Narrow QRS complex (0.09 second or less) without discernible P waves or with retrograde P waves with an abnormal axis. There is little or no variation in heart rate.

- c. Reentrant rhythms
 - i. AVRT
 - (a) Most common type of SVT
 - (b) Accessory “bypass” tract creates a cyclic reentrant pattern independent of the sinoatrial node.
 - (c) Most AV reentrant pathways conduct in a retrograde manner. Preexcitation syndromes conduct in an anterograde fashion such as in classic (or manifest) Wolff-Parkinson-White (syndrome) (WPW). ECG will show shortened PR interval and delta wave (a slurred upstroke in the QRS complex or preexcitation).
 - (d) WPW is dangerous because it may degenerate into Afib and has a risk of sudden cardiac death in children without structural heart disease.
 - ii. Atrioventricular nodal reentrant (junctional) tachycardia (AVNRT)
 - (a) Second most common type of SVT in children
 - (b) Reentry within the AV node via dual AV nodal pathways
- d. Ectopic rhythms
 - i. Rare in children
 - ii. Focal (non-reciprocating) atrial tachycardia
 - (a) Caused by abnormal catecholamine-sensitive foci with increased automaticity in the atria
 - (b) Warm-up and cool-down phases may differentiate it from other arrhythmias.
 - (c) Often resistant to pharmacologic agents
 - iii. Multifocal atrial tachycardia
 - (a) Also known as chaotic atrial tachycardia because the ventricular rate is highly irregular
 - (b) Rare in children and exact mechanism is unknown
 - iv. Junctional ectopic tachycardia
 - (a) Usually occurs within the first 48–72 hours after open-heart surgery (one of the most common arrhythmias following intracardiac repair), but can be a congenital familial arrhythmia.
 - (b) Postoperative junctional ectopic tachycardia usually resolves with supportive and pharmacologic therapy.
 - (c) Characterized by a narrow QRS complex with a rate faster than the sinus rate, usually resulting in AV dissociation and a slower atrial rate than ventricular rate
- e. Atrial flutter (AF)
 - i. Uncommon in children. AF is usually associated with structural heart disease, including myocarditis or dilated atria. AF may be a postoperative complication of CHD surgery that involves suturing through the atrial septum.
 - ii. On ECG, “saw-toothed” flutter waves are the hallmark finding. Ventricular rates depend on conduction through the AV node.
 - iii. Because of the rapid ventricular rate, cardiac output is compromised. If the AV conduction is 1:1 with a very rapid atrial rate, patients commonly present with chest pain, hypotension, and circulatory collapse.
- f. Afib
 - i. Rare in children, associated with surgical manipulation of the atria and disruption of normal conduction. Afib may also result from atrial dilation related to rheumatic heart disease or cardiomyopathies. Afib may be associated with WPW.
 - ii. The rhythm is described as “irregularly irregular.” On ECG, irregular atrial waves occur with beat-to-beat variability of atrial size and shape with normal QRS complexes.
 - iii. Afib associated with WPW can degenerate into ventricular fibrillation (VF); hence, this rhythm may be life threatening for these patients.
 - iv. Increased risk of thromboembolism

- g. Acute treatment of atrial tachyarrhythmias (see PICU I chapter)
- h. Chronic, preventive treatment of atrial tachyarrhythmias:
 - i. SVT is most common in newborns and young infants, and most of these patients will have spontaneous resolution of SVT within the first year of life. Therefore, long-term treatment with antiarrhythmic agents beyond this period may be unnecessary.
 - ii. For patients with recurrent SVT beyond 1 year of age, pharmacologic therapy may be avoided if the episodes are infrequent, self-limited, and tolerated well and if the patient has a normally structured heart and does not have preexcitation (e.g., WPW).
 - (a) Vagal maneuvers
 - (b) “Pill-in-the-pocket” therapy (single dose with a quick onset of action may be given only during an episode)
 - iii. Long-term daily therapy may be considered for patients who have frequent episodes of SVT or for patients who do not tolerate the episodes well until elective radiofrequency ablation can be done. Ablation in patients younger than 4 years or weighing less than 15 kg has a higher risk of complications, so it is generally avoided in children younger than 5 years. For older children with WPW, ablation is first-line therapy.
 - iv. Patient and arrhythmia characteristics to consider when selecting therapy:
 - (a) Age younger than 1 year: Avoid verapamil because it has caused cardiovascular collapse and death in infants.
 - (b) Cardiomyopathy or left ventricular dysfunction: Avoid (or use with extreme caution) β -blockers, calcium channel blockers, disopyramide, flecainide, and propafenone because of their potentially negative inotropic effects.
 - (c) Severe asthma: Avoid β -blockers and propafenone.
 - (d) WPW: It is recommended to avoid (or use with caution) digoxin, diltiazem, disopyramide, verapamil, and β -blockers because of their potential induction of VF with or without severe bradycardia; however, the risk depends on the type of accessory pathway and the pathway refractory period. For a refractory period shorter than 0.25 second, the risk of accelerated conduction with these agents is high. For a refractory period longer than 0.3 second, the risk of accelerated conduction is low.
 - (e) Long QT syndrome or patients taking drugs known to prolong the QT interval: Avoid (or use with caution) amiodarone, sotalol, procainamide, disopyramide, flecainide, and propafenone.
 - (f) Structural heart disease: Flecainide and propafenone have myocardial depressant and proarrhythmic effects. Although an increased incidence of cardiac arrest has been reported in pediatric patients with congenital heart defects, other retrospective analyses have shown that flecainide may be safely used in children with congenital heart defects and cardiomyopathies (Pediatr Cardiol 2015;36:146-50; Pediatr Cardiol 2017;38:1633-8). It is recommended to proceed with extreme caution when using Class Ic agents in children with structural heart disease.
- i. Recommended pharmacologic agents for specific atrial tachyarrhythmias
 - i. AVRT
 - (a) In preexcitation syndromes (e.g., WPW) with a short refractory period of accessory pathway, flecainide, propafenone, or sotalol are first line. β -Blockers may be acceptable if the refractory period is longer.
 - (b) In preexcitation syndromes (e.g., WPW), amiodarone is reserved if other drugs fail and catheter ablation is not an option or for patients with structural heart disease who are not candidates for catheter ablation (i.e., amiodarone does not exacerbate heart failure and is rarely proarrhythmic).

- (c) In concealed accessory pathways, β -blockers or non-dihydropyridine calcium channel blockers (i.e., verapamil) are first line.
 - (d) In concealed accessory pathways, flecainide or propafenone in combination with a β -blocker is a second-line option in patients with structurally normal hearts. Sotalol also is a second-line option.
 - ii. AVNRT
 - (a) β -Blockers or non-dihydropyridine calcium channel blockers (i.e., verapamil) are first line.
 - (b) Flecainide or propafenone should be added to a β -blocker as second-line therapy in patients with a structurally normal heart.
 - iii. Permanent junctional reciprocating tachycardia
 - (a) Amiodarone or verapamil (usually combined with digoxin), flecainide, or propafenone
 - (b) Flecainide or propafenone is second line.
 - iv. Junctional ectopic tachycardia
 - (a) Amiodarone is first line.
 - (b) Flecainide, procainamide, propafenone, and sotalol are alternatives (J Arrhythm 2020; 36:59-66), as well as ivabradine (JACC Clin Electrophysiol 2021;7:1052-60)
 - v. Focal atrial tachycardia
 - (a) Digoxin is first line.
 - (b) If digoxin fails, add flecainide or propafenone as second line.
 - (c) Amiodarone may be used as a second- or third-line drug.
 - vi. Multifocal atrial tachycardia
 - (a) Digoxin with flecainide or propafenone is first line.
 - (b) Amiodarone is second line.
 - vii. AF
 - (a) After achieving sinus rhythm acutely with synchronized cardioversion or transesophageal atrial overdrive pacing, recurrence of AF is unlikely, and prophylactic antiarrhythmic agents are unnecessary.
 - (b) If synchronized cardioversion or transesophageal atrial overdrive pacing is not available and the patient is stable, digoxin is first-line therapy for conversion to sinus rhythm.
 - (c) If digoxin fails, add flecainide or amiodarone as a second-line agent for conversion to sinus rhythm.
 - viii. Afib
 - (a) If the patient is stable and WPW has been excluded, propranolol or digoxin is first line for rate control.
 - (b) Second-line agents include amiodarone or sotalol, propafenone, or flecainide for rhythm control.
- 5. VT
 - a. Rare in children
 - b. Patients may present with respiratory distress or failure, signs of impending cardiovascular collapse (poor perfusion with or without hypotension), altered mental status, or a sudden collapse with rapid, weak pulses. If a pulse is present, heart rate may be normal or up to more than 200 beats/minute.
 - c. ECG: Wide QRS complex (longer than 0.09 second); may reveal monomorphic QRS complexes with absent or retrograde P waves or polymorphic (varying) QRS complexes with a QRS axis shifting back and forth around the baseline (torsades de pointes or “twisting of the points”) and AV dissociation with a ventricular rate exceeding the atrial rate
 - d. Acute treatment of VT (see PICU I chapter)

- e. Chronic, preventive treatment of VT:
 - i. Sustained VT is very rare in structurally normal hearts; hence, most patients who are converted to normal sinus rhythm will not require pharmacologic prophylaxis.
 - ii. When symptomatic, β -blockers or non-dihydropyridine calcium channel blockers (i.e., verapamil) may be used to control ventricular rate.
 - iii. If β -blockers or non-dihydropyridine calcium channel blockers (i.e., verapamil) are ineffective or if patients are severely symptomatic, flecainide or amiodarone may be used as a second-line agent.
 - iv. Phenytoin and mexiletine are additional options.
- 6. Premature ventricular contractions (PVCs)
 - a. PVCs associated with serious underlying causes may progress to VT if left untreated. Patients at high risk are those with underlying heart disease, a history of syncope, and a family history of sudden death or if the patient develops PVCs with exertion, has multiform PVCs, is symptomatic from runs of PVCs, or has frequent episodes of paroxysmal VT.
 - b. ECG: A premature, wide QRS complex with a distinct configuration that is not preceded by a P wave; a couplet is two consecutive PVCs; bigeminy is a normal QRS complex alternating with a PVC; trigeminy is a PVC every third beat; VT is three or more consecutive PVCs
 - c. Treatment of PVCs:
 - i. No treatment is needed for asymptomatic patients with isolated PVCs and normal cardiac structure and function.
 - ii. If an underlying cause is present, manage the underlying cause.
 - iii. Patients with couplets, multiform PVCs, frequent PVCs, or underlying heart disease are at risk of developing cardiopulmonary compromise and should be considered for treatment with lidocaine 1 mg/kg/dose intravenously, followed by a 20-to 50-mcg/kg/minute intravenous infusion. The Cardiac Arrhythmia Suppression Trial did not show a decrease in the risk of sudden death with treatment of PVCs (in some cases, the risk increased), so treat cautiously.
 - iv. All patients should avoid stimulants (e.g., caffeine, pseudoephedrine, methamphetamines).
- 7. VF
 - a. VF is life threatening. It is characterized by chaotic, irregular ventricular contractions with inadequate perfusion.
 - b. Signs and symptoms: Sudden collapse
 - c. ECG: QRS complexes with varying sizes and configurations with a rapid, irregular rate
 - d. Treatment of VF (see PICU I chapter):
- 8. Long QT syndrome
 - a. Long QT syndrome is a hereditary (cardiac channelopathy) or acquired condition of delayed ventricular repolarization, characterized by prolongation of the QT interval (QT interval corrected for heart rate of at least 450 milliseconds for males and at least 460 milliseconds for females) on ECG. Long QT syndrome can degenerate into VF and sudden death.
 - b. Congenital long QT syndrome often presents in childhood, with patients 9–15 years of age having frequent episodes of syncope. Acquired long QT syndrome usually presents later in adulthood and is commonly caused by medications and electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, and hypocalcemia).
 - c. Syncope may be caused by exertion, loud noises, or intense emotion. A history of syncope caused by physical exertion is a risk factor for developing VF and sudden death.
 - d. Torsades de pointes is the hallmark dysrhythmia of long QT syndrome. Because cardiac output is impaired during this polymorphic VT, the patient often develops syncope or seizures. Although spontaneous return of consciousness usually occurs after the syncopal episode, the dysrhythmia still has the potential for fatal consequences.

- e. Long QT syndrome should be ruled out for patients with a history of syncope triggered by exertion, stress, or emotion or associated with chest pain or palpitations. Additional history suggestive of long QT syndrome includes a first-degree relative with long QT syndrome, a carrier for one of the genetic mutations associated with this cardiac channelopathy, a family history of syncope, seizures, sudden death, sudden infant death syndrome, or unexplained near-drowning.
 - f. Acute treatment of long QT syndrome: For torsades de pointes, patients should be given magnesium sulfate 25–50 mg/kg (maximum 2 g) intravenously/intraosseously over 10–20 minutes (with a pulse) or as a bolus dose (without a pulse). For acquired QT interval prolongation, correction of the underlying disorder or discontinuation of the offending medication(s) is of paramount importance.
 - g. Chronic treatment of long QT syndrome:
 - i. β -Blockers (e.g., propranolol, atenolol, or nadolol) are first-line agents shown to decrease mortality from 71% in untreated patients to 6% in treated patients.
 - ii. An implantable cardioverter-defibrillator may be considered for high-risk patients such as those who do not respond effectively to β -blockers or those in whom β -blockers are contraindicated (e.g., in severe asthma).
 - iii. Restriction from competitive sports (not recreational) and avoidance of loud noises, emotionally stressful situations, and dehydration are recommended.
 - iv. Avoidance of medications that may prolong the QT interval, such as:
 - (a) Antiarrhythmics (amiodarone, sotalol, procainamide, flecainide, and propafenone)
 - (b) Antidepressants (amitriptyline, fluoxetine)
 - (c) Antiemetics (droperidol, ondansetron)
 - (d) Antifungals (ketoconazole, voriconazole)
 - (e) Antimicrobials (erythromycin, azithromycin, trimethoprim/sulfamethoxazole)
 - (f) Antipsychotics (chlorpromazine, haloperidol, quetiapine, risperidone)
 - v. A quick resource for determining the potential of drugs for prolonging the QT interval may be found at www.torsades.org (www.crediblemeds.org).
- C. Bradyarrhythmias
- 1. Caused by depression of the sinus node or abnormalities in the conduction system. Hypoxemia is the most common cause of bradycardia in children. Bradycardia also may be associated with vagal stimulation or an acute increase in intracranial pressure. Congenital or acquired complete heart block is also a common cause of significant bradycardia in the pediatric population.
 - 2. Acute treatment of bradycardia (see PICU I chapter)
 - 3. Chronic, preventive treatment of bradyarrhythmias
 - a. A permanent cardiac pacemaker is indicated for certain patients (e.g., patients with sick sinus syndrome, patients with second-degree Mobitz type II or third-degree AV block, and neonates with signs of heart failure and persistent bradycardia below 55 beats/minute).
 - b. Recent guidelines for cardiac pacing are available from the American College of Cardiology/AHA Task Force on Practice Guidelines.

Table 5. Pharmacologic Agents for Arrhythmias

Drug	Adverse Effects	Monitoring	Special Considerations
Adenosine	- Heart block and other arrhythmias - Bronchospasm - Facial flushing - Diaphoresis - Nausea - Dizziness - Headache - Dyspnea - Hyperventilation	- ECG - Heart rate - Blood pressure - Respiratory rate	- Use rapid flush two-syringe technique - Avoid in second- or third-degree AV block or sick sinus syndrome without a cardiac pacemaker - Digoxin or verapamil may worsen AV block or cause ventricular arrhythmias - Reduce dose with dipyridamole or carbamazepine, or with a transplanted heart (exaggerated response because of denervation of the transplanted heart) - Increase dose with caffeine or theophylline - Avoid in asthma because of bronchoconstriction
Digoxin	- Bradycardia - First-degree AV block - VF with WPW	- Heart rate - ECG - Renal function - Serum electrolytes - Consider serum concentrations for special circumstances (addition of interacting medication e.g., amiodarone)	- Delayed onset of action, so generally not used for acute SVT - Beware drug-drug interactions (e.g., amiodarone, flecainide, propafenone, and quinidine) (consider reducing dose by 25%–50% and increase monitoring) - Avoid hypokalemia; beware medications that alter potassium (e.g., loop diuretics)
Ivabradine	- Bradycardia - Heart block - Afib - Visual impairment - Hypertension	- ECG - Heart rate - Negative pregnancy test	- Hazardous drug/teratogen; use PPE - Substrate of CYP3A4 (major) - Beware drug-drug and food-drug interactions, avoid other drugs that prolong the QT interval (increased risk for torsades de pointes) or negative chronotropes (increased risk for heart block) - Oral solution only available through a specialty pharmacy
Class I Antiarrhythmics (sodium channel blockers)			
Class Ia Procainamide	- Hypotension - Rash - Hypersensitivity reactions - Blood dyscrasias - SLE-like syndrome including anaphylaxis (excipient)	- ECG - Blood pressure - CBC - ANA - Renal function - Hepatic function	- Avoid in second- or third-degree heart block without a cardiac pacemaker, torsades de pointes, heart failure, or SLE - May cause increased ventricular conduction with AF or Afib - Adjust dose in renal and hepatic dysfunction - Beware drug-drug interactions - Avoid drugs that prolong the QT interval or class Ia/III antiarrhythmics - Monitor ECG vs. levels - Consider alternative if ANA becomes positive; discontinue if SLE symptoms occur

Table 5. Pharmacologic Agents for Arrhythmias (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Class Ia Disopyramide	• AV block, QRS and QT prolongation, proarrhythmias (VT, VF, and torsades de pointes) • Heart failure • Hypotension • Syncope • Headache • Rash • GI upset • Low glucose and potassium • High cholesterol and triglycerides • Urinary retention • Blurred vision • Dyspnea • Agranulocytosis, thrombocytopenia	• ECG • Blood pressure • Heart rate • Serum potassium, glucose, cholesterol, triglycerides • Renal function • Liver enzymes • Serum concentration	• Avoid in second- or third-degree heart block without a cardiac pacemaker, cardiogenic shock, long QT syndrome, heart failure, or hypotension • Discontinue if QRS widens > 25% or QT is prolonged > 25% from baseline • Use with caution in AF (risk of 1:1 AV conduction and cardiovascular collapse) • Adjust dose in renal dysfunction • Beware drug-drug interactions • Avoid drugs that prolong the QT interval, are proarrhythmic, or have negative inotropic effects
Class Ib Lidocaine	• Hypersensitivity reactions • Agitation • Disorientation • Seizures • Coma • Arrhythmia • Bradycardia • Heart block • Hypotension • Bronchospasm • Respiratory depression	• ECG • Blood pressure • Respiratory rate • Serum concentrations with IV infusion	• Avoid use in WPW, Adams-Stokes syndrome (syncopal attacks), or with severe SA, AV, or intraventricular heart block without a cardiac pacemaker • CNS adverse effects more common at high serum concentrations • Beware drug-drug interactions

Table 5. Pharmacologic Agents for Arrhythmias (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Class Ib Phenytoin	• Severe hypersensitivity (including Stevens-Johnson syndrome and DRESS) • Blood dyscrasias • Hepatotoxicity • Osteoporosis • Gingival hyperplasia • Hypertrichosis • “Purple glove syndrome” • Dizziness • Drowsiness • Headache • Blurred vision • SLE	• ECG • Blood pressure • Heart rate • CBC • Liver enzymes • Vitamin D concentrations • Bone mineral density • Free serum concentrations	• Avoid use in sinus bradycardia, SA block, second- and third-degree AV block, and Adams-Stokes syndrome • Hypotension, heart block, VT, or VF with rapid administration • Beware drug-drug interactions • Free level preferred to total level
Class Ib Mexiletine	• Angina, chest pain, palpitations • AV block • Blood dyscrasias • Dizziness • Headache • Unsteady gait, incoordination • Rash • Gastric upset • Blurred vision • Tinnitus • Dyspnea	• ECG • Heart rate • CBC • Liver enzymes • Renal function • Serum concentrations	• Avoid use in patients with second- or third-degree heart block without a cardiac pacemaker • Avoid medications or dietary supplements that acidify urine (increases renal excretion) • Adjust dose for renal and hepatic dysfunction • Beware drug-drug interactions

Table 5. Pharmacologic Agents for Arrhythmias (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Class Ic Flecainide	• Sinus node dysfunction • Tachycardia • Syncope • Prolonged PR, QT, and QRS intervals • Ventricular arrhythmias • Anxiety • Dizziness • Headache • Nervousness • Tinnitus • Vertigo • Paresthesias • Tremor • Blurred vision • Dyspnea • Blood dyscrasias	• ECG • Heart rate • CBC • Liver enzymes • Serum concentrations	• Avoid use in second- or third-degree AV block or right bundle branch block without a cardiac pacemaker • Avoid use in cardiogenic shock, myocardial depression, heart failure, or a structurally abnormal heart • Avoid use in long QT syndrome • Higher risk of proarrhythmia at higher doses and chronic Afib • Beware drug-drug interactions and avoid other drugs that prolong the QT interval • Beware potential CYP2D6 genetic polymorphism-related toxicity • In infants, avoid giving with milk or milk-based formulas; dose reduction may be necessary when milk consumption decreases
Class Ic Propafenone	• First-degree AV block • Prolonged PR, QRS, and QT intervals • Proarrhythmias (VF, VT, torsades de pointes, asystole) • Palpitations • Chest pain • Positive ANA • Agranulocytosis • Dizziness • Headache • Ataxia • Nausea • Dyspepsia • Unusual metallic taste • Blurred vision • Dyspnea	• ECG • Blood pressure • Heart rate	• Avoid use in SA, AV, or intraventricular conduction disorders without a cardiac pacemaker • Avoid use in sinus bradycardia, cardiogenic shock, uncompensated heart failure, significant hypotension, bronchospasm, and structural heart disease • Reduce dose if QRS widens or second- or third-degree heart block occurs • Beware drug-drug interactions • Avoid drugs that prolong the QT interval or class Ia/III antiarrhythmics • Bradycardia worse when used with β-blockers • Consider alternative if ANA become positive; discontinue if SLE symptoms occur

Table 5. Pharmacologic Agents for Arrhythmias (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Class II Antiarrhythmics (β-blockers)			
Esmolol		• Blood pressure • Heart rate • ECG	• Withdrawal effects may occur when discontinued • Hypotension is common and more likely with doses >200 mcg/kg/min • Use with caution in patients with bronchospastic disease (e.g., nonallergic bronchospasm or chronic bronchitis) • Use with caution in patients with peripheral vascular disease (e.g., Raynaud) • Use with caution in WPW • Avoid with severe bradycardia, AV block, sick sinus syndrome • May mask signs of hypoglycemia
Propranolol		• Blood pressure • Heart rate • ECG • Blood glucose	• Use with caution in WPW (severe bradycardia requiring a cardiac pacemaker or VF) • Avoid use in severe bradycardia, second- or third-degree AV block, or sick sinus syndrome • Beware specific drug-drug interactions with amiodarone, disopyramide, propafenone, lidocaine
Atenolol		• Blood pressure • Heart rate • ECG	• Use with caution in WPW • Avoid with severe bradycardia, AV block, sick sinus syndrome • Beware specific drug-drug interactions with amiodarone, disopyramide
Nadolol		• Blood pressure • Heart rate • ECG	• Use with caution in WPW (severe bradycardia requiring a cardiac pacemaker or VF) • Avoid use in severe bradycardia, second- or third-degree AV block, or sick sinus syndrome • Adjust dose with renal dysfunction • Beware drug-drug interactions, including amiodarone, disopyramide, and propafenone

Table 5. Pharmacologic Agents for Arrhythmias (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Class III Antiarrhythmics			
Amiodarone	• Bradycardia • AV block • Heart failure • Hypotension • Proarrhythmias (prolonged QT, torsades de pointes, VT, Afib, asystole, PEA) • Pulmonary toxicity • Liver toxicity • Optic neuropathy/neuritis • Blurred vision • Visual halos • Hyperthyroidism • Hypothyroidism • Photosensitivity • Blue-gray skin discoloration • Hypersensitivity reactions	• ECG • Blood pressure • Heart rate • Chest radiograph • PFTs, oxygen saturation, blood gases, symptoms of pulmonary toxicity (dyspnea, wheezing, nonproductive cough, pleuritic pain, hemoptysis, weight loss, fever, malaise) • Liver enzymes • TFTs, symptoms of thyroid dysfunction (change in weight, lethargy, edema of hands and feet) • Ophthalmic examinations, including funduscopy and slit-lamp	• Avoid use in SA or AV conduction disorders without a cardiac pacemaker • Avoid use in sinus bradycardia, cardiogenic shock, bradycardia-induced syncope, long QT syndrome, or hypersensitivity to iodine • Fatalities caused by pulmonary toxicity, liver toxicity, severe hypotension, or thyrotoxicosis • Adjust dose or discontinue if liver enzymes > 3 times normal or double from an elevated baseline • Beware drug-drug interactions • Avoid drugs that prolong the QT interval or class Ia/Ic/III antiarrhythmics • Avoid grapefruit, pomegranate, and star fruit products • ECG effects with IV administration immediate, but complete antiarrhythmic effects not seen for several days to months
Sotalol	• QT prolongation • Bradycardia • Heart block • Hypotension • Worsening heart failure • Chest pain • Palpitations • Syncope • Proarrhythmias (sustained VT, torsades de pointes, VF) • Dizziness • Headache • Rash • Diaphoresis • Gastric distress • Musculoskeletal pain • Visual disturbance • Dyspnea	• ECG (continuously for 3 days after starting drug and with dose changes) • QT interval • Heart rate • Blood pressure • Renal function • Serum potassium • Serum magnesium	• Avoid use in SA or AV conduction disorders without a cardiac pacemaker • Avoid use in sinus bradycardia, cardiogenic shock, uncontrolled heart failure, long QT syndrome, and asthma • Evaluate baseline QT interval and renal function before initiating therapy • Use with extreme caution if corrected QT interval is > 500 ms • Reduce dose if corrected QT interval is > 550 ms • Do not abruptly discontinue therapy; taper gradually over 2 wk • Use with caution in patients with bronchospastic disease • May mask symptoms of hypoglycemia; use with caution in diabetes • Adjust dose for renal dysfunction • Avoid drugs that prolong the QT interval and other class I/III antiarrhythmics • Bradycardia enhanced with other β-blockers, CCBs, digoxin • May enhance lidocaine effects

Table 5. Pharmacologic Agents for Arrhythmias (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Class IV Antiarrhythmics (non-dihydropyridine CCBs)			
Verapamil	• AV block • Bradycardia • Heart failure • Flushing • Hypotension • Dizziness • Headache • Constipation • Nausea • Dyspepsia • Gingival hyperplasia • Rash • Elevated liver enzymes • Dyspnea • Paresthesias • Flu-like syndrome	• ECG • Blood pressure • Heart rate • Liver enzymes	• Avoid with heart failure, hypotension, or cardiogenic shock • Avoid in VT or with SA or AV node dysfunction without a cardiac pacemaker • Use with extreme caution in WPW • Avoid use in infants < 1 yr because of the risk of cardiac arrest • Adjust dose for renal dysfunction • Adjust dose by 70% for severe hepatic dysfunction • Beware drug-drug interactions (e.g., digoxin) • Avoid drugs with negative inotropic or bradycardic effects • Avoid grapefruit, pomegranate, and star fruit products

AF = atrial flutter; Afib = atrial fibrillation; ANA = antinuclear antibodies; AV = atrioventricular; CBC = complete blood count; CCB = calcium channel blocker; DRESS = drug reaction with eosinophilia and systemic symptoms; ECG = electrocardiogram; IV = intravenous; GI = gastrointestinal; ms = millisecond(s); PEA = pulseless electrical activity; PFT = pulmonary function test; SA = sinoatrial; SLE = systemic lupus erythematosus; SVT = supraventricular tachycardia; TFT = thyroid function test; VF = ventricular fibrillation; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White (syndrome).

Patient Cases

Questions 13–15 pertain to the following case.

S.B. is a 2-month-old boy who presents to the ED with a history of poor feeding, turning blue around the mouth during feeding, sweating while feeding, and severe irritability. Vital signs are as follows: temperature 98.6°F (37°C), blood pressure 100/60 mm Hg, and heart rate 280 beats/minute. He is alert and active, does not appear to be in respiratory distress, is not mottled, and has a capillary refill of less than 2 seconds. An ECG is ordered immediately, which reveals a narrow QRS complex (less than 0.09 second) without discernible P waves and no variation in heart rate.

13. Which is best to initially manage S.B.'s SVT?

- Ice water to the face.
- Synchronized cardioversion.
- Propranolol.
- Adenosine.

Patient Cases (*continued*)

14. S.B. is successfully treated. He is admitted to the hospital for a further workup that includes an ECHO, which reveals no structural abnormalities. A few hours after the test is completed, his mother calls the nurse because S.B. is not waking up to feed, and his color is dusky. When the nurse assesses him, she notes that he appears to have difficulty breathing, his heart rate is too fast to count, his pulses are weak and thready, and he has pale, cool extremities with a poor capillary refill. She calls the emergency response team. When you arrive, his ECG reveals a heart rate of 320 beats/minute with a narrow QRS complex. Which would be most appropriate for treating S.B.'s SVT at this time?
- A. Ice water to the face.
 - B. Synchronized cardioversion.
 - C. Propranolol.
 - D. Adenosine.
15. After S.B. receives the selected intervention, he has a shortened PR interval and delta wave (a slurred upstroke in the QRS complex or preexcitation) on ECG after conversion to normal sinus rhythm. Which first-line agent is most appropriate to chronically manage his WPW?
- A. Propranolol.
 - B. Digoxin.
 - C. Verapamil.
 - D. Flecainide.
16. G.A. is a 15-year-old male adolescent who presents to the cardiology clinic with a 2-day history of subjective fever, shortness of breath, and cough producing watery sputum. His medical history is significant for idiopathic Afib, for which he takes propranolol and amiodarone. At the clinic, his temperature is 100.4°F (38°C) and respiratory rate is 22 breaths/minute. Heart rate and blood pressure are within normal limits for age and sex. Overall, he appears well hydrated and is able to drink fluids. On physical examination, the only pertinent findings are crackles over his left lung field without wheezes. A chest radiograph is ordered, which reveals patchy left lower lobe consolidation. Which antibiotic would be best to treat G.A.'s presumed atypical pneumonia?
- A. Azithromycin.
 - B. Doxycycline.
 - C. Levofloxacin.
 - D. Cefdinir.

V. ANTICOAGULATION

- A. Signs and Symptoms of Thrombosis
 - 1. Inability to draw blood back from catheters
 - 2. Difficulty flushing or infusing medications or fluids through catheters
 - 3. Edema or venous congestion of an extremity (venous thrombus)
 - 4. Increased chest wall veins or caput medusa; increased abdominal veins (superior or inferior vena cava thrombus)
 - 5. Decreased perfusion, loss of pulse, coldness of an extremity, signs of emboli to toes or fingers (arterial thrombus)
 - 6. Facial, neck, or upper arm swelling; prominent neck veins; cyanosis (superior vena cava syndrome)

B. Consequences of Thrombosis

1. Arterial (systemic) thrombosis may lead to stroke, limb ischemia, or the inability to access an artery for diagnostic or therapeutic cardiac catheterization. Complete occlusion of a systemic-to-PA shunt is fatal if not relieved immediately.
2. Venous (pulmonary) thrombosis may lead to pulmonary embolism or prevent essential cardiac catheterizations because of thrombi in the veins of the upper or lower body.
3. In patients with endovascular stents (to relieve either arterial or venous obstruction), thrombosis of the stent is life threatening.

C. Recommendations for Antithrombotic and Fibrinolytic Therapy in Heart Disease**1. Stroke**

- a. The AHA and the American Stroke Association published an updated guideline for management of stroke in neonatal and pediatric patients in 2019.
- b. Neonates and children with arterial ischemic stroke caused by cardioembolism:
 - i. Unfractionated heparin
 - ii. Low-molecular-weight heparin or warfarin
 - iii. Continue for 3–6 months or longer
 - iv. Alteplase may be considered if within 4.5 hours from onset, age greater than 2 years, persistent focal deficit, proven infarct and arterial occlusion on imaging, and no contraindications (Pediatr Neurol 2016;56:8-17).
- c. Low-dose aspirin for 2 years or longer, depending on the underlying condition and risk of recurrent stroke

2. Central venous lines

- a. Maintain only the central lines that are essential.
- b. Flush with normal saline or heparin to maintain patency. Alteplase to restore line patency for obstructed central lines (repeat dose if line patency not restored in at least 30 minutes). If the patient does not respond to two doses of alteplase, use imaging to rule out central line–associated thrombus.
- c. Anticoagulation is recommended for symptomatic central-line associated thrombus. Anticoagulation may or may not be recommended for asymptomatic central-line associated thrombus (depends on individual patient factors). Central lines should be removed after 3–5 days of therapeutic anticoagulation (Chest 2012;141:e737S-e801S); however, timing of anticoagulation and removal should be individualized based on patient's specific factors, such as ongoing need for central line access, risk of progressive thrombosis versus surgical removal (Blood Adv 2018;2:3292-316).
- d. Prevention of central-line associated thrombosis with low-dose intravenous heparin until central line removal:
 - i. For planned Fontan procedure
 - ii. With concomitant bacteremia
 - iii. For hypercoagulable risk (e.g., history of thrombosis, thrombophilia, or increased Hct) (Circulation 2013;128:2622-703).
- e. Low-molecular-weight heparin or unfractionated heparin, followed by low-molecular-weight heparin or vitamin K antagonist, should be continued for a total of 6 weeks to 3 months. If the central line is still in place at the end of therapeutic anticoagulation, a prophylactic dose of anticoagulation (low-molecular-weight heparin with target anti-Xa concentrations 0.1–0.3 unit/mL or warfarin with target INR 1.5–1.9) should be continued until the central line is removed. If thrombosis recurs during prophylactic anticoagulation, therapeutic dosing should be initiated and maintained until the central line is removed and for at least 3 months.
- f. Thrombolytic therapy should not be used in neonates unless major vessel occlusion is causing critical compromise of organs or limbs. If thrombolysis is necessary, alteplase is the agent of choice and should be given after fresh frozen plasma (plasminogen).

3. Pulmonary embolism
 - a. Agents:
 - i. Unfractionated heparin or low-molecular-weight heparin for at least 5 days (may be longer)
 - ii. Warfarin
 - (a) Initiate as early as day 1.
 - (b) Discontinue unfractionated heparin or low-molecular-weight heparin on day 6 (or later if INR is 2 or lower).
 - b. Duration of anticoagulation:
 - i. 3 months for thrombus associated with resolved risk factor (e.g., removal of central line or repair of CHD)
 - ii. If the patient has ongoing risk factors, continue in either therapeutic or prophylactic doses until the risk factors have resolved.
 - iii. 6–12 months for idiopathic thrombus
 - c. Special considerations:
 - i. Rapid removal by thrombolytics, pulmonary embolectomy, or stent placement if life-threatening cardiorespiratory compromise occurs
 - ii. Vena cava filter if anticoagulation is contraindicated in stable heart disease and pulmonary embolism (or anticoagulation failed)
4. Systemic-to-PA shunts
 - a. Synthetic shunts:
 - i. Low-dose aspirin, unless increased risk of bleeding
 - ii. Complications from low-dose aspirin in neonates unknown
 - b. Early postoperative period after a synthetic shunt: Low-dose heparin infusion (usually 10 unit/kg/hour), if no concerns for surgical bleeding
 - c. Early postoperative period after a synthetic shunt if increased risk of thrombosis:
 - i. Risks – Stented shunt, hypercoagulable state, known central line–associated thrombosis, or suspected or confirmed infection
 - ii. Systemic heparinization
 - d. If thrombosis of synthetic shunt suspected:
 - i. Immediate systemic heparinization (50- to 100-unit/kg intravenous loading dose with consideration of a maintenance intravenous infusion)
 - ii. Increase systemic blood pressure to improve flow through shunt (i.e., epinephrine or phenylephrine)
 - iii. Maximize oxygen delivery while decreasing oxygen demand
 - iv. Intubation
 - (a) Mechanical ventilation
 - (b) Neuromuscular blockade
 - v. Anticipate cardiac catheterization, shunt revision, or extracorporeal membranous oxygenation (ECMO).
 - e. Sustained high risk of thrombosis (e.g., a hypercoagulable state): Anticoagulant with antiplatelet (e.g., low-molecular-weight heparin plus low-dose aspirin or clopidogrel)
 - f. If a chronically draining pleural effusion of significant volume is present, monitor anticoagulation carefully, and adjust with neurology input if a cerebral venous infarct develops.
 - g. Systemic thrombolysis (e.g., with alteplase) is not recommended for synthetic systemic-to-PA shunts because of the risk of bleeding and potential need for catheterization, surgical intervention, or ECMO. There is no recommendation for a catheter-directed thrombolytic.
5. Palliated single ventricle
 - a. Assess risk factors for thrombosis, and correct or minimize, if possible. Do serial clinical assessments because risk factors may change over time. Appropriate diagnostic imaging is necessary to assess for thrombosis (e.g., transthoracic or transesophageal ECHO, magnetic resonance imaging).

- b. Long-term antiplatelet therapy after superior cavopulmonary anastomosis or the Fontan procedure is reasonable.
 - c. Warfarin or low-molecular-weight heparin may be reasonable for 3–12 months after the Fontan procedure.
 - d. Long-term warfarin (beyond 12 months) after the Fontan procedure may be reasonable if anatomic or hemodynamic risk factors are present (e.g., hypoplastic cardiac chambers with flow stasis, ventricular dysfunction, arrhythmia, abnormal thrombophilia profile).
 - e. If risk factors change or develop during the patient's course, changing from an antiplatelet to an anticoagulant or targeting higher concentrations should be considered.
6. Prosthetic valves
- a. Prevention of thrombosis

Mechanical Aortic/Mitral Valves
Low-dose aspirin with warfarin (goal INR 3) Exception: Aortic valves > 6 mo, no risk factors ^a = warfarin (goal INR 2.5)
On-X Aortic Valve, No Risk Factors^a (Prevention)
Low-dose aspirin with warfarin (goal INR 2.5; range 2–3); > 3 mo = low-dose aspirin with warfarin (goal INR 1.5–2)
Bioprosthetic Aortic/Mitral Valves
Low-dose aspirin with warfarin (goal INR 2.5) Exception: Valves > 6 mo, no risk factors ^a = low-dose aspirin
Bioprosthetic Pulmonary Valves
No treatment
Prosthetic Tricuspid Valves
Low-dose aspirin with warfarin (goal INR 2–3) Exception: Valves > 3–6 mo, no risk factors ^a = low-dose aspirin

^aRisk factors include previous thromboses, systemic ventricular dysfunction, hypercoagulable condition, and Afib.

- b. For patients immediately after valve placement who have no clinical concerns for postoperative bleeding, unfractionated heparin or low-molecular-weight heparin is suggested as a bridge to therapeutic INR with warfarin (when warfarin is indicated). Heparin may be continued until INR is therapeutic for 2 consecutive days.
 - c. For patients with contraindications to warfarin, low-dose aspirin should be used to prevent thrombosis in mechanical or bioprosthetic valves, as necessary.
 - d. Treatment of prosthetic valve thrombosis
 - i. For right-sided prosthetic valves, unfractionated heparin. Alteplase if thrombus persists
 - ii. For left-sided prosthetic valves, slow infusion of low-dose alteplase or emergency thrombectomy (depends on patient specific factors and capability of facility to perform procedures)
 - iii. After resolution of a prosthetic valve thrombus, unfractionated heparin and warfarin should be initiated. Heparin may be discontinued after warfarin is therapeutic according to institutional guidelines. Goal INR with an aortic valve is 3–4 and 3.5–4.5 with a mitral valve. All patients should receive aspirin in addition to warfarin.
7. Heparin-induced thrombocytopenia
- a. Direct thrombin inhibitors (e.g., argatroban, bivalirudin, fondaparinux)
 - b. Heparinoid (e.g., danaparoid) – Not available in the United States

D. Antithrombotic and Fibrinolytic Agents

1. Extensive drug tables that include mechanism of action, indications, contraindications, dosing, monitoring, and adverse effects for antithrombotic and fibrinolytic agents in infants, children, and adolescents have been published previously and may be found in the AHA guidelines for the prevention and treatment of pediatric patients with CHD and acquired heart disease and in the American College of Chest Physicians guidelines for antithrombotic therapy in neonates and children. Additional considerations are below.
2. Anticoagulants
 - a. Warfarin
 - i. Neonates and infants: The AHA guideline does not recommend warfarin for children younger than 1 year unless needed for prophylaxis of a mechanical valve.
 - ii. Drug-drug and drug-herbal interactions
 - iii. Recommend consistent daily dietary intake of vitamin K
 - (a) Difficult for infants. Breastmilk contains little vitamin K, but infant formulas contain it. Oral vitamin K supplement may be used in breastfeeding infants.
 - (b) Dark leafy green vegetables and cooking oils are two of the highest sources of vitamin K in a typical diet. Cooking oils have varying amounts of vitamin K, with corn oil being one of the lowest and soybean oil being one of the highest. Processed foods and foods from fast food restaurants typically contain soybean oil. There also may be differences in vitamin K content between fresh and frozen prepared vegetables.
 - iv. Genetic polymorphisms
 - (a) Genetic variants of *VKORC1* and *CYP2C9* may affect warfarin activity.
 - (1) Polymorphisms in *VKORC1* may lead to warfarin resistance and the need for higher doses to maintain goal INR values, or polymorphisms may lead to warfarin sensitivity and the need for lower doses to avoid bleeding.
 - (2) Variant alleles of the *CYP2C9* enzymes (*CYP2C9*2* and *CYP2C9*3*) lead to the reduced clearance of warfarin and the need for lower doses to maintain goal INR values and prevent bleeding.
 - (b) Warfarin dosing algorithms that incorporate genotypes are not validated in the pediatric population. Consider genetic testing for *VKORC1* and *CYP2C9* variants in patients who are difficult to treat.
 - v. Point-of-care INR monitoring
 - (a) Devices vary but usually require minimal blood to do the test and produce INR results within 1 minute.
 - (b) Quality assurance requires that point-of-care INR values be compared with laboratory-based INR values every 6–12 months or after test strips are changed.
 - vi. Patient safety
 - (a) Medication management standards of The Joint Commission accrediting organization address the initiation and maintenance of anticoagulation therapy as an important patient safety initiative.
 - (1) The standards state that organizations should use approved protocols for starting, maintaining, and reversing anticoagulation, as well as assessing for possible drug-drug interactions.
 - (2) For warfarin, a baseline and a current INR should be used to monitor and adjust therapy.
 - (3) Dietary services should be notified to assess for food-drug interactions.
 - (4) Prescribers, staff, and patients and their families should be educated on anticoagulation therapy. Patients and families should be taught the importance of follow-up monitoring, adherence issues, dietary restrictions, and the potential for adverse drug reactions and interactions (www.jointcommission.org).

- b. For heparin-induced thrombocytopenia: Argatroban, bivalirudin, fondaparinux
 - c. Target specific oral anticoagulants: Dabigatran, rivaroxaban, apixaban, edoxaban (clinical trials ongoing with information available at www.clinicaltrials.gov)
 - i. Rivaroxaban: FDA approved (less than 18 years of age) for treatment and prevention of recurrent venous thromboembolism after at least 5 days of initial treatment with parenteral anticoagulants per the EINSTEIN-Jr. study (Lancet Haematol 2020;7:e18-27). FDA approved (2 years of age or older) for thromboprophylaxis following the Fontan procedure per the UNIVERSE study (J Am Heart Assoc. 2021;10:e021765a).
 - ii. Dabigatran: FDA approved (3 months of age or older) for treatment of venous thromboembolism after at least 5 days of initial treatment with parenteral anticoagulants or prevention of recurrent clots after completion of treatment for first venous thromboembolism per the DIVERSITY study (Lancet Haematol 2021; 8:e22-33).
- E. Periprocedural Anticoagulation
- 1. Interrupting long-term maintenance anticoagulation (usually with warfarin) to do invasive procedures may place patients at risk of developing a thrombus.
 - 2. “Bridging” refers to the period when patients are transitioned off long-term maintenance anticoagulation (often onto shorter-acting anticoagulation) to prepare for a procedure and then transitioned back to long-term maintenance anticoagulation.
 - 3. No studies have compared bridging schedules; therefore, no optimal regimen has been identified. Furthermore, individual patient characteristics must be considered when designing bridging regimens because patients have different risk factors for clotting or bleeding.
 - 4. The following is a sample published bridging regimen:
 - a. Low risk of thrombus (i.e., receiving anticoagulation post-Fontan procedure; stable)
 - i. Discontinue warfarin 3–5 days before procedure.
 - ii. Do not start an alternative anticoagulant preprocedure.
 - iii. Check INR on day before or on day of procedure.
 - iv. Do not initiate alternative anticoagulant postprocedure.
 - v. Resume warfarin at standard maintenance dose on the night of procedure.
 - b. Medium risk of thrombus (i.e., receiving anticoagulation for cardiomyopathy, central line, or prosthetic valve; thrombus more than 3 months after diagnosis)
 - i. Discontinue warfarin 5 days before procedure.
 - ii. Check INR 3 days after discontinuing warfarin.
 - iii. Initiate enoxaparin when the INR is below 2, and discontinue after the morning dose on day before the procedure.
 - iv. Resume enoxaparin on the evening of procedure day, if patient is not at risk of bleeding (if bleeding is a concern, resume enoxaparin on the morning of day after procedure).
 - v. Resume warfarin at standard maintenance dose on the evening of day after procedure unless contraindications are present.
 - vi. Check INR 3 days after reinitiating warfarin, and titrate to goal INR.
 - vii. Discontinue enoxaparin when INR is above 2.
 - c. High risk of thrombus (i.e., receiving anticoagulation for PHN; history of pulmonary embolus, recurrent thrombosis, prosthetic valve thrombosis, homozygous protein C deficiency; thrombus less than 3 months after diagnosis)
 - i. Discontinue warfarin 5 days before procedure.
 - ii. Check INR 3 days after discontinuing warfarin.
 - iii. Initiate enoxaparin when INR is below 2. Check anti-Xa on day 2 of bridging therapy with goal 0.5–1 unit/mL. Discontinue after the morning dose on day before procedure.

- iv. Initiate unfractionated heparin infusion 4 hours after the last dose of enoxaparin. Check activated partial thromboplastin time (aPTT) and titrate to goal 60–80 seconds, or check anti-Xa and titrate to goal 0.35–0.7 unit/mL. Discontinue 1 hour before procedure.
- v. Resume unfractionated heparin infusion 1 hour after procedure, if not at risk of bleeding, and adjust to goal aPTT according to patient-specific needs.
- vi. Resume enoxaparin on day 2 after procedure, if patient is not at risk of bleeding (if there are bleeding concerns, continue unfractionated heparin until risk is reduced).
- vii. Resume warfarin at standard maintenance dose on day 5 after procedure unless contraindications are present.
- viii. Check INR 3 days after reinitiating warfarin, and titrate to goal INR.
- ix. Discontinue enoxaparin when INR is above 2.

F. Signs and Symptoms of Bleeding

1. Petechiae
2. Oozing from the gums or old puncture sites
3. Blood in the stool or urine
4. Nosebleeds
5. Respiratory distress, desaturation (possible hemothorax, especially if a chest tube is present in a post-operative patient)
6. Abdominal distension, pain, or tenderness (retroperitoneal hemorrhage)
7. Altered level of consciousness, hypotonia, change in quality or spontaneity of movements (intracranial hemorrhage)

Patient Cases

Questions 17–19 pertain to the following case.

G.E. is a 2-month-old girl (weight 4.2 kg) given a diagnosis of ToF with mild, intermittent right ventricular outflow tract obstruction at birth. She required admission to the pediatric ICU for a significant hypertensive crisis, and a femoral central line was placed. The femoral central line remained in place for 2 days, until she was transferred to the intermediate medical unit. It is a week later, and she is on the general medical unit with a warm, red, swollen lower extremity, and Doppler ultrasonography confirms a venous thrombosis.

17. Which is best for managing G.E.'s clot?
- A. Warfarin.
 - B. Fondaparinux.
 - C. Enoxaparin.
 - D. Unfractionated heparin.

Patient Cases (*continued*)

18. Four months later, G.E. has another hypertensive crisis and is readmitted to the pediatric ICU. She is scheduled for placement of a systemic-to-PA shunt during this hospital stay. After her surgery, which type of anticoagulation would be best for G.E.?
- A. Low-dose aspirin starting immediately postoperatively and continuing for long-term maintenance anticoagulation.
 - B. Unfractionated heparin starting immediately postoperatively and continuing for long-term maintenance anticoagulation.
 - C. Unfractionated heparin starting immediately postoperatively with transition to low-dose aspirin for long-term maintenance anticoagulation.
 - D. Unfractionated heparin starting immediately postoperatively with transition to warfarin for long-term maintenance anticoagulation.
19. G.E. presents to the ED pale, lethargic, and cyanotic 6 months after her systemic-to-PA shunt is placed. Her oxygen saturations are 70%. Thrombosis of her shunt is suspected. In addition to intubation and mechanical ventilation, which is best for emergently managing a clot in G.E.?
- A. Unfractionated heparin.
 - B. Enoxaparin.
 - C. Alteplase.
 - D. Bivalirudin.

Questions 20 and 21 pertain to the following case.

A.V. is a 16-year-old female adolescent with no significant medical history who went to her primary care physician with ear pain. After receiving a diagnosis of acute otitis media, she was given an injection of ceftriaxone in her left hip. She had persistent pain in her left hip after the injection and had difficulty walking and bearing weight on her left leg. On the day of admission, she felt dizzy and nauseated, had double vision, and passed out. When she awoke, her mother took her to the ED, where a scan was positive for large bilateral pulmonary emboli with evidence of heart failure. She was given a bolus of heparin and initiated on a heparin infusion. After transfer to the pediatric ICU, she remains hemodynamically stable on a heparin infusion. The results of an ECHO are within normal limits.

20. Which is best for managing A.V.'s anticoagulation at this time?
- A. Continue heparin to complete 5 days of therapy.
 - B. Continue heparin, and transition to warfarin to complete 6 months of therapy.
 - C. Continue heparin, and initiate alteplase to complete 5 days of therapy.
 - D. Continue heparin, and transition to aspirin to complete 6 months of therapy.
21. Which would be the most appropriate treatment for A.V. if she presented with significantly increased work of breathing, tachypnea, tachycardia, and jugular venous distension and her ECHO revealed evidence of right heart failure?
- A. Continue heparin for 5 days of therapy.
 - B. Continue heparin, and transition to warfarin to complete 6 months of therapy.
 - C. Continue heparin, and initiate alteplase to complete 5 days of therapy.
 - D. Continue heparin, and transition to aspirin to complete 6 months of therapy.

Patient Cases (*continued*)

22. S.P. is a 16-year-old male adolescent (weight 95 kg) who had a prosthetic mitral valve placed 2 years ago. He was maintained on low-dose aspirin but developed a thrombus 4 months after the valve surgery. He currently receives warfarin 12 mg on Monday, Wednesday, Friday, and Sunday and 9 mg on Tuesday, Thursday, and Saturday, with INR values of 2.02–2.44. He is visiting the anticoagulation clinic in preparation for knee surgery next week. Which is the most appropriate treatment plan for S.P.'s anticoagulation?
- Discontinue warfarin 5 days before surgery, and resume warfarin at a higher dose on the day of surgery.
 - Discontinue warfarin 5 days before surgery, and resume warfarin at the former dose on the day of surgery.
 - Discontinue warfarin 5 days before surgery, bridge with enoxaparin, resume warfarin at the former dose on the day after surgery, and discontinue enoxaparin on the day after surgery.
 - Discontinue warfarin 5 days before surgery, bridge with enoxaparin, resume warfarin at the former dose on day 5 after surgery, and discontinue enoxaparin when INR is above 2.
23. L.L. is a 22-month-old girl (weight 12 kg) who just had tricuspid valve replacement. She does not have right ventricular dysfunction or other risk factors for clotting. She is expected to receive low-dose aspirin and warfarin therapy for 3–6 months after her procedure. Her baseline INR the day of surgery was 1.1. She received one dose of warfarin 1 mg, and the following day, her INR was 1.7. The medical resident ordered her next warfarin dose as 1.5 mg because her INR had changed by only 0.6. Which is most appropriate for L.L.'s next warfarin dose?
- Give warfarin 1.5 mg.
 - Give warfarin 1 mg.
 - Give warfarin 0.5 mg.
 - Hold warfarin.

VI. PULMONARY HYPERTENSION

- Etiology
 - Definition of PHN:
 - Mean PA pressure 20 mm Hg or higher at rest or at least 30 mm Hg or higher with exertion (normal PA pressure 12–16 mm Hg or about 20% of systemic mean arterial pressure) *or*
 - Systolic PA pressure greater than one-half of the systolic systemic pressure according to ECHO
 - PHN may develop because of primary lung disease that affects the pulmonary vasculature or lung tissue and development, or it may be secondary to other disease states that cause alterations in pulmonary vascular tone, mechanical stresses on the pulmonary vessels, and/or structural remodeling of the lung vasculature and tissue.
- Clinical Features and Diagnosis
 - Infants with persistent PHN of the newborn commonly have cyanosis with hepatomegaly, an active right ventricle on palpation, and a loud pulmonary second sound on auscultation.
 - Children with idiopathic PHN commonly present with breathlessness, poor appetite, failure-to-thrive, lethargy, tachycardia, and irritability.
 - Functional capacity, and hence severity of PHN, is assessed according to a modification of the World Health Organization (WHO) classification:
 - Class I: No limits on physical activity (i.e., ordinary activity does not result in dyspnea, fatigue, chest pain, or near syncope)

- b. Class II: Slight limits on physical activity (i.e., no symptoms at rest, but ordinary activity results in dyspnea, fatigue, chest pain, or near syncope)
 - c. Class III: Marked limits on physical activity (i.e., no symptoms at rest, but less-than-ordinary activity results in dyspnea, fatigue, chest pain, or near syncope)
 - d. Class IV: Major limits on physical activity (i.e., dyspnea and/or fatigue may be present at rest; any activity results in symptoms and increased discomfort) and signs of right heart failure
 - 4. Patients may be stratified into risk categories to define treatment goals.
 - a. Lower risk:
 - i. WHO functional class I/II
 - ii. No failure-to-thrive
 - iii. No evidence of right heart failure
 - iv. No syncope
 - v. Minimally elevated brain natriuretic peptide concentrations
 - vi. Mean PA pressure/mean systolic arterial pressure ratio below 0.5 (0.5–0.75 may be considered intermediate risk)
 - b. Higher risk:
 - i. WHO functional class III/IV
 - ii. Poor height and weight z-score at presentation
 - iii. Mean PA pressure/mean systolic arterial pressure ratio above 0.75
 - iv. Clinical and ECHO evidence of right ventricular failure
 - v. Syncope
 - vi. Greatly elevated brain natriuretic peptide concentrations
 - vii. Progression of symptoms
- C. Pathophysiology
- 1. Increased vascular tone or vasoreactivity
 - 2. Vascular endothelial injury caused by mechanical forces or stresses
 - 3. Vascular smooth muscle hypertrophy
- D. Treatment Strategies
- 1. Initial: oxygen, analgesics, diuretics, alkalization, and anticoagulation (if minimal bleeding risk)
 - 2. Long-term:
 - a. Augmentation of nitric oxide
 - i. Inhaled nitric oxide (increases levels of cyclic guanosine monophosphate)
 - ii. Sildenafil, tadalafil, vardenafil (phosphodiesterase type 5 inhibitors to prevent the breakdown of cyclic guanosine monophosphate)
 - b. Augmentation of prostacyclin
 - i. Epoprostenol (intravenous and inhaled prostacyclin analog)
 - ii. Treprostinil (intravenous, inhaled, subcutaneous, and oral prostacyclin analog)
 - iii. Iloprost (inhaled prostacyclin analog)
 - iv. Selexipag (oral selective prostacyclin IP receptor agonist)
 - c. Inhibition of endothelin 1
 - i. Bosentan (non-selective endothelin A and endothelin B receptor antagonist)
 - ii. Ambrisentan (selective endothelin A receptor antagonist)
 - iii. Macitentan (nonselective endothelin A and endothelin B receptor antagonist)
 - d. Combinations of prostacyclin analogs, phosphodiesterase inhibitors, and endothelin receptor antagonists are often used in the pediatric population when clinical deterioration occurs despite maximal doses with one agent, but combination therapy is not well studied. There is no clear consensus regarding the most effective and safe combinations.

3. Smooth muscle–based therapy also may decrease pulmonary vasoconstriction. Calcium channel blockers (only if patient responds to vasoreactivity study; not often used first line because of the low response rate to vasodilator testing and conversion from responders to non-responders over time)
 - a. Nifedipine
 - b. Amlodipine
 - c. Diltiazem
 4. Right ventricular function may be improved by reducing pulmonary afterload with agents that promote pulmonary vasodilation, optimize right ventricular volume, augment right ventricular contractility, and maintain left ventricular contractility and systemic vascular resistance (because of ventricular interdependence).
- E. Management of Acute PHN
1. Prompt treatment is required for children who present with syncope, right heart failure, or postoperative pulmonary arterial hypertension or in patients with significant decompensation after withdrawal of therapy to manage pulmonary hypertension (e.g., low oxygen saturation, PA to systemic artery pressure ratio greater than 0.75, signs of low cardiac output).
 2. Initial management with oxygen, analgesics, diuretics, and alkalinization may be necessary to treat acute pulmonary vasoconstriction related to hypoxemia, pain, or acidosis, but these are temporizing measures. Consider anticoagulation in patients with low cardiac output syndrome or hypercoagulable state (weigh risk of thrombosis against risk of bleeding).
 3. Inhaled nitric oxide is currently a first-line treatment to rapidly reduce PA pressure in patients with newly diagnosed severe PHN or in postoperative PHN. One advantage of inhaled nitric oxide is its ability to vasodilate PAs without affecting systemic arteries.
 4. Intravenous or inhaled epoprostenol has been used to reduce PA pressure in patients with inadequate response to inhaled nitric oxide.
 5. ECMO (cardiopulmonary bypass) may be necessary in patients when other modalities fail. Patients with severe respiratory or cardiac disease in addition to PHN are more likely to progress to ECMO.
- F. Chronic Management of PHN
1. Main references – AHA and American Thoracic Society (ATS) guideline published in 2015 and the 2019 European Consensus statement
 2. Treatment algorithm for children
 - a. Initial supportive measures and expert referral, a cardiac catheterization is done to confirm diagnosis.
 - b. Acute vasoreactivity test, usually with inhaled nitric oxide
 - i. “Responders”
 - (a) Drop in mean PA pressure by 20% with normal or unchanged cardiac output or decrease in the ratio of pulmonary to systemic vascular resistance per modified Barst criteria
 - (b) 20% decrease in pulmonary vascular resistance to systemic vascular resistance ratio without a drop in cardiac output per AHA/ATS
 - c. “Nonresponders”
 - i. Surgical repair: Left-to-right shunt from CHD
 - ii. Calcium channel blockers
 - (a) Idiopathic PHN
 - (b) Repaired CHD if greater than 1 year old
 - (c) Contraindicated if less than 1 year old with right-sided heart failure
 - iii. Fail calcium channel blockers: Single agent from the following classes: endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, or prostacyclin analogs (inhaled iloprost or treprostinil)

- iv. Fail single agent: add agent from one or both remaining classes
- v. Fail combination: Add parenteral prostacyclin
- vi. Fail parenteral prostacyclin: atrial septostomy to decompress right heart or reverse Potts shunt (left pulmonary artery to descending aorta)
- vii. Fail all measures:
 - (a) Lung transplant
 - (b) Reserved for children with less than a 50% chance of 2-year survival without transplant
 - (c) Also consider if still WHO functional class III or IV on optimal therapy or rapidly progressing disease
- d. “Non-responders” to vasodilator testing at lower risk (as defined in section 4.a., above)
 - i. Single agent from one of the following classes: endothelin receptor antagonists or phosphodiesterase type 5 inhibitors.
 - ii. Fail single agent: Add agent from other class
 - iii. Fail combination and still lower risk: Add inhaled prostacyclin
 - iv. Fail inhaled prostacyclin: Switch to parenteral prostacyclin
 - v. Fail parenteral prostacyclin: Atrial septostomy or reverse Potts shunt
 - vi. Fail all measures: Lung transplant
- e. “Non-responders” to vasodilator testing at higher risk (as defined in section 4.b., above)
 - i. Parenteral prostacyclin first-line; strongly recommended to combine with endothelin antagonist and phosphodiesterase type 5 inhibitor (better long-term survival).
 - ii. Success (asymptomatic and near normal pulmonary hemodynamics): Switch to oral/inhaled prostacyclin.
 - iii. Failure:
 - (a) Atrial septostomy
 - (b) Reverse Potts shunt
 - iv. Fail all measures: Lung transplant
- f. Continuous repeat evaluation for progression of disease and response to targeted treatment is critical for treating these patients.

Table 6. Pharmacologic Agents for PHN

Drug	Adverse Effects	Monitoring	Special Considerations
Inhaled nitric oxide	• Methemoglobinemia • Airway injury from nitrogen dioxide • Rebound PHN • Contraindicated in right-to-left shunts • Contraindicated in left ventricular dysfunction	• VS • Pulmonary hemodynamics • ABG • Methemoglobin concentrations • Inspired nitric dioxide	• Must have proper dose calibration and immediate access to a backup supply to avoid acute discontinuation • Wean slowly • Nitrogen dioxide • > 3 ppm or methemoglobin > 7% may respond to reduced dose or discontinuation • Methemoglobinemia may require methylene blue, IV vitamin C, or blood transfusion

Table 6. Pharmacologic Agents for PHN (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Amlodipine	• Hypotension • Peripheral edema • Headache • Constipation • Nausea • Vomiting • Flushing • Tachycardia • Dizziness • Gingival hyperplasia	• Pulmonary hemodynamics • Heart rate • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life	• Beware drug-drug and food-drug interactions
Nifedipine	• Hypotension • Peripheral edema • Headache • Constipation • Nausea • Vomiting • Flushing • Tachycardia • Dizziness • Gingival hyperplasia • GI obstruction in at-risk patients with extended-release dosage forms	• Pulmonary hemodynamics • Heart rate • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life	• Do not use in children < 1 yr (negative inotropic effects) • Do not crush, chew, or divide extended-release products • Beware drug-drug and food-drug interactions
Diltiazem	• Bradycardia • Second- or third-degree heart block • Hypotension • Peripheral edema • Headache • Constipation • Nausea • Vomiting • Flushing • Dizziness • Gingival hyperplasia • Acute hepatic injury • Contraindicated with accessory bypass tract (e.g., WPW)	• Pulmonary hemodynamics • Heart rate • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life • Liver function	• Do not use in children < 1 yr (negative inotropic effects) • Do not crush, chew, or divide extended-release products (exception: Taztia XT and Tiazac capsules may be opened and sprinkled on applesauce for immediate use) • Beware drug-drug interactions • Grapefruit juice may affect drug concentrations, but this may not be clinically relevant. Monitor clinically

Table 6. Pharmacologic Agents for PHN (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Sildenafil	• Flushing • Dizziness • Headache • Nausea • Abdominal discomfort • Epistaxis • Acute hearing loss • Not recommended in pulmonary veno-occlusive disease • Visual changes	• Pulmonary hemodynamics • Heart rate • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life	• Beware drug-drug interactions • Beware food-drug interactions • Dose adjustment for CrCl < 30 mL/min/1.73 m² • FDA warning against use in children in 2012 as a result of STARTS-1 and STARTS-2 trials that suggested lack of benefit for low doses and increased mortality with high doses and longer duration of therapy. Since then, multiple reviews of trial data have suggested that these findings may be related to stochastic aberrations. Risk-benefit assessment should be performed to determine if use is necessary.
Tadalafil	• Headache • Nausea • Myalgia • Nasal congestion • Flushing • Allergic reaction • Not recommended in pulmonary veno-occlusive disease	• Pulmonary hemodynamics • Heart rate • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life	• Beware drug-drug interactions • Beware food-drug interactions • Dose adjustment for CrCl 31–80 mL/min/1.73 m² • Avoid use with CrCl < 30 mL/min/1.73 m²
Bosentan	• Serious hepatic injury including liver failure • Teratogenicity • Male infertility • Dose-related decreases in Hgb/Hct • Not recommended in pulmonary veno-occlusive disease	• Pulmonary hemodynamics • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life • Baseline and monthly liver enzymes • Clinical signs and symptoms of liver injury • Baseline, 1 mo, and 3 mo Hgb/Hct and every 3 mo thereafter • Negative pregnancy test before starting therapy, every month after starting therapy, and 1 mo after discontinuing therapy in females of childbearing potential	• Hazardous drug/teratogen; use PPE • Females of childbearing potential should not split, crush, or handle broken tablets • Compounded suspension recipe now available with 1-mo stability • If patients are to use tablets for doses and cannot swallow the tablet intact, may dissolve intact tablets in water (no acidic solutions [e.g., fruit juices]). Solution from tablets is for single use; discard remainder • Beware drug-drug interactions • Beware food-drug interactions • Adjust for hepatic dysfunction • REMS program with restricted access; only available outpatient through www.bosentanrems.com

Table 6. Pharmacologic Agents for PHN (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Ambrisentan	• Hepatic injury reported, but probably owing to other causes • Teratogenicity • Male infertility • Dose-related decreases in Hgb/Hct • Not recommended in pulmonary veno-occlusive disease	• Pulmonary hemodynamics • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life • Liver enzymes when clinically indicated • Baseline, 1 mo, and periodic Hgb/Hct • Negative pregnancy test before starting therapy, every month after starting therapy, and 1 mo after discontinuing therapy in females of childbearing potential	• Hazardous drug/teratogen; use PPE • Swallow tablet whole; do not split, crush, or chew • Females of childbearing potential should not split, crush, or handle broken tablets • Minor substrate of CYP2C9 and CYP3A4, P-glycoprotein, and hepatic glucuronidases • Beware drug-drug interactions; much less risk than bosentan • Beware food-drug interactions; much less risk than bosentan • Adjust dose for hepatic dysfunction • REMS program with restricted access for female patients; only available outpatient through www.ambrisentanrems.us.com
Macitentan	• Hepatic injury reported • Teratogenicity • Decreases in Hgb/Hct • Peripheral edema and fluid retention • Not recommended in pulmonary venoocclusive disease	• Pulmonary hemodynamics • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life • Liver enzymes when clinically indicated • Baseline, 1 month, and periodic Hgb/Hct • Negative pregnancy test before starting therapy, every month after starting therapy, and 1 month after discontinuing therapy in females of childbearing potential	• Hazardous drug/teratogen; use PPE • Swallow tablet whole; do not split, crush, or chew • Females of childbearing potential should not split, crush, or handle broken tablets • Major substrate of CYP3A4, minor substrate of CYP2C9, CYP2C19 • Beware drug-drug interactions • Beware food-drug interactions • REMS program with restricted access for female patients; only available outpatient through www.opsumitrems.com

Table 6. Pharmacologic Agents for PHN (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Epoprostenol	• Thrombosis and central line infection • Life-threatening rebound PHN • Jaw pain • Bone pain • Headaches • Rashes • Thrombocytopenia • Anxiety • Agitation • Diarrhea • Vomiting • Diaphoresis • Flu-like syndrome • Should not be used in CHF and left ventricular systolic dysfunction • Should not be used in pulmonary veno-occlusive disease	• Pulmonary hemodynamics • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life • Infusion delivery system to prevent drug interruption	• Dedicated central line required • Do not mix or co-infuse with other medications or IVF • Because of the risk of severe rebound PHN, infusion must not be interrupted • Backup infusion cassettes and pumps required • Closed-hub system may decrease infection rate • Tachyphylaxis and dose escalations are common • Flolan must be diluted with approved diluent • Veletri may be diluted with sterile water or NS
Treprostinil	• Thrombosis and central line infection • Life-threatening rebound PHN • Hypotension • Thrombocytopenia • Pain at SC injection site • Should not be used in CHF and left ventricular systolic dysfunction • Should not be used in pulmonary veno-occlusive disease	• Pulmonary hemodynamics • Blood pressure • Exercise capacity • Exertional dyspnea • Fatigue • Syncope • Chest pain • Quality of life • Infusion/inhalation delivery system to prevent drug interruption	• May be infused SC or by dedicated central line • Do not mix or co-infuse with other medications or IVF • Use in-line 0.22 or 0.2 micron filter for IV • Rotate SC infusion site every 3 days, local hot and cold packs, or topical/PO analgesics may help pain • Inhalation requires the Tyvaso Inhalation System • Because of risk of severe rebound PHN, infusion/inhalation must not be interrupted • Backup infusion cassettes, pumps, inhalation systems required • Administer oral tablets with food (250 calorie, moderate to medium fat) • Swallow tablets whole; do not split, crush, or chew • Adjust dose for significant hepatic dysfunction • May be diluted with NS, sterile water, or approved diluent

Table 6. Pharmacologic Agents for PHN (*continued*)

Drug	Adverse Effects	Monitoring	Special Considerations
Iloprost	- Life-threatening rebound PHN - Headache - Cough - Bronchospasm - Dizziness - Hypotension - Thrombocytopenia - Syncope - Should not be used in CHF and left ventricular systolic dysfunction - Should not be used in pulmonary veno-occlusive disease	- Pulmonary hemodynamics - Blood pressure - Exercise capacity - Exertional dyspnea - Fatigue - Syncope - Chest pain - Quality of life - Inhalation delivery system to prevent drug interruption	- Inhalation requires the I-neb ADD device - Backup inhalation systems required - Use limited by adverse effects, frequency of inhalations, and clinical deterioration
Selexipag	- Diarrhea - Nausea - Headache - Jaw pain - Pulmonary edema - Not recommended in pulmonary venoocclusive disease	- Pulmonary hemodynamics - Blood pressure - Exercise capacity - Exertional dyspnea - Fatigue - Syncope - Chest pain - Quality of life - Liver enzymes when clinically indicated	- Dilute in NS and glass vials - Protect from light - Do not filter - Entire dose must be infused within 4 hours of vial reconstitution - Swallow tablets whole; do not split, crush, or chew - Adjust dose for significant hepatic dysfunction - Major substrate of CYP2C8, minor substrate of CYP3A4 - Beware drug-drug interactions

ABG = arterial blood gas; ADD = adaptive aerosol delivery; CHF = congestive heart failure; CrCl = creatinine clearance; GI = gastrointestinal; Hgb = hemoglobin; Hct = hematocrit; IV = intravenous; IVF = intravenous fluid; NS = normal saline; PHN = pulmonary hypertension; PO = oral(ly); PPE = personal protective equipment; REMS = Risk Evaluation and Mitigation Strategy; SC = subcutaneously; VS = vital signs; WFW = Wolff-Parkinson-White (syndrome).

Patient Cases

24. W.L. is a 4-year-old boy (height 38 inches [96 cm] [5th percentile for age and sex], weight 13.8 kg) who “passed out” on the playground at day care. He has a 2-month history of being very despondent and tired, according to his mother, and he becomes “breathless” when playing with other children. He has cardiomegaly and pulmonary congestion on chest radiography. An ECHO reveals a mean PA pressure/systemic artery pressure ratio of 0.9 and right ventricular hypertrophy but no CHD, so he is scheduled for cardiac catheterization as part of a workup for PHN. During catheterization, his PA pressure does not drop in response to inhaled nitric oxide. Which is best for W.L.?
- A. Nifedipine.
 - B. Iloprost.
 - C. Epoprostenol.
 - D. Sildenafil.
25. M.M. is a 14-year-old male adolescent (height 67 inches [171 cm] [75th percentile for age and sex], weight 63.2 kg) with a history of dyspnea and fatigue with chest pain on physical exertion. An ECHO reveals a PA pressure of 75 mm Hg. Cardiac catheterization confirms a diagnosis of PHN. During vasodilator testing, his PA pressure decreases by 15 mm Hg. Which would be the best first-line treatment for M.M.’s PHN?
- A. Diltiazem.
 - B. Bosentan.
 - C. Nifedipine.
 - D. Sildenafil.
26. L.P. is a 2-year-old girl (height 36 inches [92 cm] [90th percentile for age and sex], weight 14 kg) with idiopathic PHN (WHO functional class II) who has been taking oral sildenafil 25 mg four times daily for the past 2 months. Her mean PA/systemic artery pressure ratio was 0.6 at the beginning of therapy and is now 0.58. Which would be the most appropriate next step in treating L.P.?
- A. Increase oral sildenafil.
 - B. Add oral bosentan.
 - C. Add inhaled treprostinil.
 - D. Add intravenous treprostinil.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Immune globulin is the only proven therapy to reduce the incidence of CAA; hence, it should be part of initial therapy, making Answers C and D incorrect. However, several factors may place this patient at high risk of developing CAA and possibly immune globulin failure: age older than 9 years, male sex, incomplete KD presentation, and thrombocytopenia during the acute phase of illness. This patient also had a baseline echocardiogram that revealed coronary artery dilatation; therefore, corticosteroids should be considered as first-line therapy with immune globulin and medium-dose aspirin for this patient. The AHA now states that adding prednisolone to immune globulin for patients at high risk appears to substantially reduce the incidence of coronary artery anomalies (Answer B is correct; Answer A is incorrect).

2. Answer: D

This patient has a large aneurysm, which places him at a higher risk of developing thrombosis. Low-dose aspirin plus low-molecular-weight heparin or warfarin (goal INR 2–3) would be indicated at this time (Answer D correct). High-dose aspirin is not indicated for prevention of thrombosis with aneurysms (usually given until patients are afebrile for 48–72 hours) making Answer A incorrect. Additionally, antiplatelet therapy alone is insufficient to prevent thrombosis with large aneurysms making Answers B and C incorrect.

3. Answer: A

Although this patient already developed CAA during the acute phase of illness, IVIG and medium-dose aspirin are still appropriate, making Answer A correct. The patient's initial therapy with IVIG has not failed; therefore, infliximab and cyclosporine are not indicated at this time (Answers B and C are incorrect). Alteplase is a thrombolytic and would only be of benefit if the patient had an established thrombus (Answer D is incorrect).

4. Answer: D

For patients who do not respond to the initial dose of immune globulin, the most common second-line therapy is a repeated dose of immune globulin. However, this patient developed renal dysfunction after the initial immune globulin treatment. Because she had a significant adverse event that was probably related to immune globulin, an alternative second-line agent

is recommended, making Answers A–C incorrect. Although infliximab is now the most common third-line agent for patients who have two doses of immune globulin, it has also been used successfully as a second-line agent in place of a second dose of immune globulin (Answer D is correct).

5. Answer: C

This patient should receive an annual influenza vaccine, regardless of her history of KD (Answers A and B are incorrect). For patients with KD specifically, both influenza and varicella vaccinations are recommended to limit the risk of developing Reye syndrome from an active viral illness during salicylate therapy. The patient will be committed to aspirin therapy until her aneurysm regresses; thus, she should be vaccinated, making Answer C correct and Answer D incorrect. Because patients may not mount a complete immune response to live vaccines after high-dose immune globulin, it is recommended that they be revaccinated 11 months after immune globulin. Because injectable influenza vaccine is an inactivated virus, there are no restrictions with administering the vaccine in relation to immune globulin, and there is no need for repeat immunization other than the second dose of vaccine to complete the series for this 6-month-old infant.

6. Answer: A

This patient has developed rebound hypertension after intervention for CoA. Manipulation of the aorta during catheter or surgical procedures may lead to stimulation of the sympathetic nervous system and RAAS causing the hypertension. Accordingly, hypertension in this setting responds best to β -blockers or ACEIs (or possibly ARBs), making captopril the best choice for long-term management of her blood pressure in a non-intensive care unit setting (Answer A is correct; Answers B, C, and D are incorrect).

7. Answer: A

This patient is having a hypercyanotic spell related to her ToF. Initial management involves simple measures (e.g., providing knee-to-chest positioning to increase systemic vascular resistance, providing supplemental oxygen, and relaxing the child if the spell was triggered by anxiety or agitation). Morphine would be appropriate to reduce the child's anxiety. Morphine also

relaxes infundibular spasm, which probably caused this patient's hypercyanotic spell (Answer A is correct). Modest fluid boluses (5–10 mL/kg) to increase systemic vascular resistance may be effective as well. Propranolol is appropriate if the patient does not respond to more benign measures, making Answer C incorrect. Phenylephrine is considered last-line therapy because of the risk of adverse effects, particularly with prolonged infusions (Answers B and D are incorrect).

8. Answer: C

The patient should visit a dentist regularly starting at 1–3 years of age, according to the American Dental Association and the American Academy of Pediatrics, making Answer A incorrect. However, this patient is at risk of bacterial endocarditis because she has cyanotic CHD that has not been fully repaired and has a prosthetic shunt (Answer B is incorrect). Amoxicillin is the first-line oral antibiotic for prophylaxis against bacterial endocarditis, making Answer C correct and Answer D incorrect. Amoxicillin should be administered 30–60 minutes before any invasive dental procedure that is likely to produce bacteremia.

9. Answer: C

This patient probably has acute toxicity from methamphetamine ingestion (i.e., “ecstasy”), including blood pressure above 120/80 mm Hg. Phentolamine is a nonselective α -adrenergic blocker that is preferred for managing hypertension secondary to cocaine or amphetamine/methamphetamine toxicity (Answer C is correct). Phentolamine may be given as intermittent bolus doses every 5 minutes until blood pressure is controlled and every 1–4 hours thereafter. Nitroprusside would be an alternative agent, but it requires continuous intravenous infusion and might pose a risk of toxicity if high doses or prolonged use were necessary (Answer A is incorrect). Esmolol is contraindicated in amphetamine/methamphetamine-induced hypertension because it will worsen the crisis, given its unopposed action on α -adrenergic receptors, making Answer B incorrect. Oral therapy with enalapril would be inappropriate for an acutely intoxicated patient, making Answer D incorrect.

10. Answer: A

This patient has renal disease and CHF in addition to hypertension. Angiotensin-converting enzyme inhibitors might not help preserve renal function in this patient

because she is already dialysis-dependent; however, ACEIs reduce afterload and are the drugs of choice for CHF (Answer A is correct). Although β -blockers may be beneficial in managing CHF because of their ability to limit sympathetic overactivity and reduce cardiac remodeling long term, they are contraindicated in the setting of acute decompensated heart failure (Answers C and D are incorrect). Nicardipine is a good agent to manage hypertensive emergencies, but it is not a good choice in acute decompensated heart failure because of its negative inotropic effects (Answer B is incorrect).

11. Answer: C

The patient has achieved goal blood pressure values (at the 50th percentile for age, height, and sex with chronic kidney disease). However, she has developed cough as an adverse effect of enalapril (i.e., no evidence suggests that the dry, nonproductive cough is caused by pneumonia or pulmonary congestion related to heart failure), making Answers A and B incorrect. Angiotensin receptor blockers would be a good choice because she would maintain the benefit of RAAS inhibition but with a reduced chance of cough related to inhibition of bradykinin breakdown, making Answer C correct. Furosemide would offer no benefit because the patient is not volume overloaded and has no evidence of pulmonary edema, making Answer D incorrect.

12. Answer: A

Hypertension is best managed with a single agent, if possible; thus, the dose of her antihypertensive should be maximized before adding additional agents (Answer A is correct; Answers C and D are incorrect). It is highly unlikely that this patient would achieve better control of blood pressure by reducing salt intake, making Answer B incorrect.

13. Answer: A

This patient has SVT (i.e., history of difficulty feeding and irritability, heart rate exceeding 220 beats/minute, ECG with narrow QRS complex without discernible P waves, and no variation in heart rate). He is hemodynamically stable with normal blood pressure, good perfusion, no altered mental status, and no respiratory distress. In this situation, simple vagal maneuvers (e.g., ice water to the face) may be tried initially to convert the patient to normal sinus rhythm (Answer A is correct); therefore, initial treatment with adenosine and/or synchronized cardioversion is unnecessary (Answers B

and D are incorrect). Propranolol is not appropriate for acute management of SVT, making Answer C incorrect.

14. Answer: D

The patient now has signs of poor perfusion related to SVT (i.e., lethargy, respiratory distress, weak pulse, and pale/cool extremities with poor capillary refill). Vagal maneuvers could be considered, but they should not delay adenosine or synchronized cardioversion in an unstable patient, making Answer A incorrect. Synchronized cardioversion should be considered for this patient, but adenosine may still be tried first if intravenous/intraosseous access is readily available. Because the patient was previously treated for SVT and was admitted to the hospital, intravenous access is probably already established. Therefore, adenosine could be administered quickly (Answer D is correct; Answer B is incorrect). If adenosine therapy fails, synchronized cardioversion should be tried. Propranolol is not appropriate for the acute management of SVT, making Answer C incorrect.

15. Answer: D

The patient has AVRT caused by preexcitation (WPW), as indicated by the short PR interval and delta wave on ECG after adenosine. Digoxin, β -blockers, and non-dihydropyridine calcium channel blockers (e.g., verapamil and diltiazem) may cause severe bradycardia and induce VF in WPW and are generally avoided unless the refractory period of the accessory pathway is longer than 0.3 second, making Answers A–C incorrect. Flecainide is considered a first-line agent for WPW in patients with structurally normal hearts and would be a good choice for this patient because the refractory period of his pathway is unknown, making Answer D correct. Propafenone, sotalol, and amiodarone are alternative agents.

16. Answer: B

The most likely pathogens for this patient's pneumonia are *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, which are covered by doxycycline (Answer B is correct). *Streptococcus pneumoniae*, which is not covered well by doxycycline, is still a possibility. But given the patient's age and milder presentation, infection with this pathogen is less likely. Azithromycin and levofloxacin are appropriate for atypical pathogens, but they should be avoided with amiodarone because of the potential for QT-interval prolongation, making

Answers A and C incorrect. Cefdinir does not interact with amiodarone and is an appropriate empiric coverage for *S. pneumoniae*, but it does not cover atypical pathogens (Answer D is incorrect). A combination of doxycycline and cefdinir would also cover all of these organisms.

17. Answer: C

This patient has a clot that probably developed secondary to a femoral central line. Enoxaparin has ample data regarding safety, efficacy, monitoring, and dosing adjustment in infants; hence, it is appropriate first-line therapy for treating clots in this patient, making Answer C correct. Fondaparinux is not a first-line option because of the limited data in infants and the lack of an appropriate dosage form for eventual outpatient therapy (i.e., enoxaparin is available in a 300 mg/3 mL multidose vial, whereas fondaparinux is available only in prefilled syringes, with the smallest being 2.5 mg), and most institutions lack ready access to a fondaparinux-based anti-Xa curve for monitoring therapy, making Answer B incorrect. Warfarin is not effective immediately and is challenging to provide to infants, making Answer A incorrect. Unfractionated heparin to achieve therapeutic aPTT values is not used on a general medical unit; hence, this patient would require transfer back to the pediatric ICU if unfractionated heparin were selected. In addition, she would probably require anticoagulation for 3 months, depending on the size of the clot and her response to therapy, making Answer D incorrect.

18. Answer: C

This patient should receive long-term anticoagulation with aspirin for her systemic-to-pulmonary shunt, making Answer C correct and Answers B and D incorrect. Because she has a history of thrombosis, it is reasonable to place her on systemic heparinization in the immediate postoperative period (Answer A is incorrect).

19. Answer: A

Emergency systemic heparinization is indicated for suspected shunt thrombosis, making Answer A correct. The inability to titrate enoxaparin quickly limits its usefulness in an emergency, making Answer B incorrect. Thrombolytic therapy is not recommended because of the high risk of bleeding in patients who will require further diagnostic procedures (e.g., cardiac catheterization) or procedures to restore patency of the shunt (e.g., surgical revision) or even cardiopulmonary support by

ECMO, making Answer C incorrect. Bivalirudin would be expected to provide immediate, titratable anticoagulation; however, data in the pediatric population are still very limited. Bivalirudin is usually reserved for heparin-induced thrombocytopenia in the pediatric population at this time, making Answer D incorrect.

20. Answer: B

This patient has idiopathic pulmonary embolism, probably as a result of a deep venous thrombosis after her antibiotic injection. She is hemodynamically stable; thus, she should be treated with systemic heparinization and transitioned to warfarin or low-molecular-weight heparin to complete at least 6 months of therapy, making Answer B correct and Answers A and D incorrect. She may require a longer duration of anticoagulation if she is determined to have a coagulation disorder or another risk factor for recurrent thromboembolism. A thrombolytic is not indicated in a patient with cardiorespiratory stability, making Answer C incorrect.

21. Answer: C

The patient has signs of cardiorespiratory instability related to her pulmonary emboli (i.e., dyspnea, tachycardia, and right-sided heart failure with jugular venous distension), so she is a candidate for thrombolytic therapy, making Answer C correct. Life-threatening cardiorespiratory compromise may require thrombectomy or stent placement. Anticoagulants and antiplatelets are not appropriate with cardiorespiratory instability, making Answers A, B, and D incorrect.

22. Answer: D

This patient is at high risk of thrombosis with a history of valvular thrombosis requiring long-term warfarin anticoagulation after his low-dose aspirin regimen has failed; thus, he should be bridged with alternative anticoagulation for his knee surgery, making Answer D correct and Answers A and B incorrect. A low-molecular-weight heparin (e.g., enoxaparin), unfractionated heparin, or a combination of the two may be used while warfarin is held. Although no standard bridging regimen exists (i.e., individual patient factors must be considered when assessing risks of clotting or bleeding), alternative anticoagulation should not be discontinued until a therapeutic INR has been achieved with warfarin (Answer C is incorrect).

23. Answer: C

This patient had a significant response to her initial warfarin dose (INR increased by 0.6). However, because it takes about 3 days to see the full response to warfarin at any given dose, she could become supratherapeutic if kept on the same loading dose, making Answer B incorrect. According to the recommended American College of Chest Physicians dosing algorithm for warfarin in children, her dose on day 2 for an INR of 1.4–1.9 should be 50% of the initial loading dose, making Answer C correct and Answers A and D incorrect.

24. Answer: C

This patient is a “non-responder” to vasodilator testing, making Answer A incorrect. He is in a higher risk category (i.e., failure-to-thrive, syncope, WHO functional class IV, PA pressure/systemic pressure ratio greater than 0.75, and right heart failure). First-line therapy should be intravenous epoprostenol or intravenous/subcutaneous treprostinil, according to the treatment algorithm from the 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension from The European Pediatric Vascular Disease Network (EPPVDN) (Answer C is correct; Answers B and D are incorrect). Combination therapy with a phosphodiesterase type 5 inhibitor and/or endothelin receptor antagonist should be considered for initial therapy as well, particularly if the combination allows for reduced doses of prostacyclin analog.

25. Answer: A

This patient is a “responder” to vasodilator testing and is older than 1 year, so first-line treatment would be a calcium channel blocker, according to the treatment algorithm from the 2019 updated consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension from The European Pediatric Vascular Disease Network (EPPVDN), making Answer A correct and Answers B and D incorrect. Diltiazem and nifedipine are both options. Diltiazem, which may have a greater effect on the pulmonary vasculature than on the systemic vasculature, has a better reduction in PA pressure than nifedipine, making Answer C incorrect. However, these effects have not been studied sufficiently to make diltiazem the calcium channel blocker of choice. Twice-daily dosing, especially for an adolescent patient, is advantageous over thrice-daily dosing. Thus, if nifedipine were selected, a better dosing option would be a 60-mg extended-release tablet given once daily.

26. Answer: B

This patient is lower risk, as evidenced by her WHO functional class, appropriate weight and height for age/sex, baseline mean PA/systemic artery pressure ratio less than 0.75, and monotherapy with a phosphodiesterase type 5 inhibitor. She has not responded to the maximum recommended dose of sildenafil (i.e., 2 mg/kg/dose four times daily), making Answer A incorrect. Adding an agent from another class (either an oral endothelin receptor antagonist or an inhaled prostacyclin analog) would be the next step after optimizing her sildenafil dose, making Answer B correct and Answer D incorrect. Given the technical requirements for a special inhalation delivery system for treprostinil and the frequency of four times daily inhalations, oral therapy with bosentan would be better (Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

The diagnosis of KD can be made on day 4 of illness in the presence of at least four principal criteria (i.e., nonpurulent conjunctivitis, cracked lips, maculopapular rash, and cervical lymphadenopathy larger than 1.5 cm for this child). Initial ECHO serves only as a baseline for the long-term treatment of patients with KD; thus, the lack of significant cardiac findings on ECHO does not rule out the need for treatment, making Answer C incorrect. Although CAA may be detected as early as 3 days from illness onset, CAAs more commonly develop in the subacute phase of illness (i.e., after fever resolves, but before resolution of all clinical features). Immune globulin is the standard of care to prevent CAA in children with KD; therefore, the AHA recommends that all children thought to have the diagnosis be treated with immune globulin. The 2017 AHA guideline recommends treatment as soon as possible within 10 days of illness after a diagnosis is made (Answer A is correct; Answer B is incorrect). A single high dose of immune globulin (2 g/kg) is preferred to a low dose (500 mg/kg) over 4 days because two meta-analyses showed a significantly lower incidence of CAA in patients receiving high-dose therapy (Answer D is incorrect). The AHA currently recommends adding either medium-dose aspirin (30–50 mg/kg/day) or high-dose aspirin therapy (80–100 mg/kg/day) for 48–72 hours after the patient is afebrile and then continuing low-dose aspirin therapy (3–5 mg/kg/day) for at least 6–8 weeks until repeat ECHO. However, use of aspirin during the acute phase of illness is controversial and varies by practice site. Although medium-dose or high-dose aspirin may shorten the duration of fever, no studies have shown a reduction in CAA with aspirin.

2. Answer: D

The child has a giant CAA (larger than 8 mm in diameter), placing him at high risk of myocardial ischemia. He also has coronary artery thrombosis. Low-dose aspirin is recommended for all patients, even in those without evidence of CAAs, for 4–6 weeks after initial onset of illness. For patients with rapidly expanding CAAs or a maximum z-score of 10 or greater, low-dose aspirin plus low-molecular-weight heparin or warfarin (goal INR 2–3) is indicated. For patients at increased risk of thrombosis (e.g., large or giant aneurysms) and a recent history of coronary artery thrombosis, triple therapy with low-dose aspirin plus a second antiplatelet agent

(e.g., clopidogrel) plus low-molecular-weight heparin or warfarin (goal INR 2–3) is indicated, making Answer D correct and Answers A–C incorrect.

3. Answer: C

This patient has CHF secondary to her VSD, as indicated by her failure-to-thrive, tachycardia, cardiomegaly, and pulmonary edema. Her left ventricular ejection fraction is normal; hence, this is probably right-sided failure, which would initially be expected with a left-to-right shunt lesion. Angiotensin-converting enzyme inhibitors reduce afterload and the workload on the heart; thus, captopril would be beneficial for this patient. A loop diuretic (e.g., furosemide) is a good first choice for reducing preload and pulmonary edema, making Answer C correct. Digoxin is not beneficial in managing right-sided heart failure without concomitant left ventricular dysfunction (Answers A and B are incorrect). β -Blockers (e.g., propranolol) may be beneficial in the long-term treatment of patients with CHF to blunt sympathetic hyperactivity and cardiac remodeling; however, this patient is expected to have surgical correction of her underlying cause for heart failure in the near future. Given the need for a prolonged titration schedule, propranolol would unlikely add benefit in the short term, making Answer D incorrect.

4. Answer: D

This patient has elevated blood pressure (i.e., average blood pressures on at least three separate occasions are above the 90th but below the 95th percentile for age, height, and sex). All patients should be counseled regarding a healthy diet and encouraged to maintain an appropriate level of physical activity, but this is especially important for this patient, whose weight is above the 99th percentile for age and sex (Answer D is correct; Answer C is incorrect). She does not require antihypertensive medication at this time. She has no family history of significant comorbid conditions, and her laboratory values show no renal disease, diabetes, or hyperlipidemia, making Answers A and B incorrect. Her weight may be contributing to her elevated blood pressure, but another possibility is white-coat hypertension. The primary care physician should do ambulatory blood pressure monitoring and initiate a diagnostic evaluation. Subspecialty referral to cardiology or nephrology may be necessary.

5. Answer: D

This patient has stage II hypertension (i.e., average blood pressures on at least three separate occasions are $\geq$ 95th percentile plus 12 mm Hg). He is posttransplantation and is being immunosuppressed with tacrolimus. Calcineurin inhibitor–induced hypertension generally responds well to calcium channel blockers, making Answer D correct. Angiotensin-converting enzyme inhibitors are good first-line agents for patients with chronic kidney disease and proteinuria; however, this patient has a newly transplanted kidney, and the protein in his urine is caused by his nephrostomy with external bag collection. He still has reduced kidney function in the graft, as evidenced by his CrCl of about 70 mL/minute/1.73 m². Angiotensin inhibitors could worsen his renal function, making Answer A incorrect. Slightly elevated blood pressures are allowed in the immediate transplant period to ensure good perfusion of the newly grafted organ, but this patient is 2 months posttransplantation, making Answer B incorrect. All patients should be counseled regarding a healthy lifestyle, including diet and exercise, but this patient requires antihypertensive therapy, especially to prolong graft survival, making Answer C incorrect.

6. Answer: B

This patient's medical history is highly suggestive of long QT syndrome (i.e., syncope on exertion and with emotional triggers). In addition, she presents with chest pain, palpitations, and a QT interval longer than 460 milliseconds. Because she has a history of syncope with exertion, she is at high risk of developing VF and sudden death. Chronic prophylactic therapy is recommended, making Answer B correct and Answer A incorrect. β -Blockers are first-line agents because they reduce mortality from 71% to 6% in patients with long QT syndrome, making Answers C and D incorrect.

7. Answer: D

Torsades de pointes is the hallmark dysrhythmia associated with long QT syndrome, making Answer D correct and Answers A–C incorrect. Because cardiac output is impaired during this polymorphic VT, the patient often develops syncope or seizures. Although spontaneous return of consciousness usually occurs after the syncope episode, dysrhythmia still has the potential for fatal consequences.

8. Answer: C

This patient has signs of heparin-induced thrombocytopenia (i.e., extension of the clot despite a therapeutic anti-Xa concentration, decline in Plt, and positive anti-heparin antibody screen). All heparin products (unfractionated heparin infusion, heparin flushes, and low-molecular-weight heparin) should be discontinued, making Answers A, B, and D incorrect. The patient should be initiated on a short-acting alternative anticoagulant therapy for her existing clot (e.g., argatroban, bivalirudin, or fondaparinux). Argatroban is a direct thrombin inhibitor that may be used to treat this patient, making Answer C correct.

9. Answer: B

Anticoagulation with warfarin is appropriate for the first 3 months in left-sided valve placements. The goal INR for bioprosthetic (tissue) valves is lower (2–3) than for mechanical prosthetic valves (2.5–3.5), making Answers A and C incorrect. Because this patient has no risk factors for thrombosis (i.e., no left ventricular dysfunction, history of thrombosis, hypercoagulable disorder, or Afib), he may transition to low-dose aspirin after 3 months, making Answer B correct and Answer D incorrect. If he had risk factors, he would continue on warfarin therapy.

10. Answer: D

Inhaled nitric oxide is currently a first-line treatment to rapidly reduce PA pressure in patients with newly diagnosed severe PHN or in postoperative PHN, making Answer B incorrect. The initial dose may be 20 ppm with weaning once oxygenation improves. Doses should not exceed 20 ppm for prolonged periods because of the risk of methemoglobinemia and elevation in the toxic metabolite nitrogen dioxide, making Answer A incorrect. Because the patient had rising PA pressures despite inhaled nitric oxide at 20 ppm, additional therapy should be used versus maintaining high-dose, prolonged inhaled nitric oxide. Although inhaled iloprost is as beneficial as inhaled nitric oxide in the acute care setting, this medication requires a special delivery system that may be technically difficult to initiate in the immediate postoperative period after cardiac surgery. Similarly, oral therapy with sildenafil and bosentan would not be good in the immediate post-cardiac surgery patient (Answer C is incorrect). Epoprostenol infusion can manage PHN in the postoperative setting and can quickly be titrated to effect, making Answer D correct.

11. Answer: B

Bosentan may cause hepatotoxicity, including acute liver failure. Monthly liver enzymes are required as part of the Bosentan REMS Program. Registration and compliance with REMS requirements are necessary to receive bosentan on an outpatient basis from a specialty pharmacy. This patient has experienced some clinical symptoms of hepatic dysfunction, so bosentan should be discontinued and the patient further evaluated for liver dysfunction (Answer B is correct; Answers A, C, and D are incorrect). Ambrisentan, a selective endothelin A receptor antagonist, may be an option in the future. Although ambrisentan carries the same potential risk of hepatotoxicity as bosentan, recent trials have not shown it to cause elevations in liver enzymes or clinical signs or symptoms of liver dysfunction. More data will be required to determine whether this reduced risk of liver dysfunction continues.

PULMONARY

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Learning Objectives

1. Design an optimal treatment regimen for pediatric patients with asthma.
2. Discuss the role of pharmacologic therapies for status asthmaticus.
3. Assess and recommend treatment for a patient with cystic fibrosis (CF).
4. Review the management of CF-related comorbidities, including CF-related diabetes and pancreatic insufficiency.
5. Design a treatment regimen for community-acquired pneumonia in pediatric patients.

Abbreviations in This Chapter

AFB	Acid-fast bacilli
CAP	Community-acquired pneumonia
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
DPI	Dry powder inhaler
FEV ₁	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
HFA	Hydrofluoroalkane
ICS	Inhaled corticosteroid
LABA	Long-acting β -agonist
MDI	Metered dose inhaler
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
MSSA	Methicillin-susceptible <i>S. aureus</i>
NHLBI	National Heart, Lung, and Blood Institute
NTM	Nontuberculous mycobacteria
SABA	Short-acting β -agonist

Self-Assessment Questions

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

1. A previously healthy 8-year-old girl is admitted to the hospital with pneumonia. She is febrile and requires oxygen. The patient attends school, her immunizations are up to date, and she lives at home with her two older siblings. Which is the best empiric treatment for the patient's pneumonia?
 - A. Amoxicillin.
 - B. Ampicillin.
 - C. Ceftriaxone.
 - D. Clindamycin.
2. A 4-year-old boy presents to his pediatrician with wheezing and upper respiratory congestion. His medical history is significant for prematurity (36 weeks), eczema, and recurrent pneumonia. The patient lives at home with his parents and two older siblings (one of his siblings was given a diagnosis of asthma at age 5). Which best reflects the part of the patient's history that is a major risk factor for asthma?
 - A. Sibling with asthma.
 - B. Prematurity.
 - C. Age.
 - D. Eczema.
3. A 5-year-old boy (weight 15 kg) with cystic fibrosis (CF) was admitted to the hospital for an acute pulmonary exacerbation. He is allergic to penicillins – hives – and his previous respiratory cultures have grown *Pseudomonas aeruginosa*, methicillin-susceptible *Staphylococcus aureus* (MSSA), and *Haemophilus influenzae*. Which is the best antibiotic regimen for empiric coverage?
 - A. Piperacillin/tazobactam 2250 mg intravenously every 8 hours and tobramycin 150 mg intravenously every 24 hours.
 - B. Meropenem 600 mg intravenously every 8 hours alone.
 - C. Cefepime 750 mg intravenously every 8 hours and tobramycin 150 mg intravenously every 24 hours.
 - D. Ceftriaxone 750 mg intravenously every 24 hours and tobramycin 150 mg intravenously every 24 hours.
4. A 15-year-old, previously healthy female adolescent was admitted to the hospital yesterday for nausea and vomiting. Today, she spikes a fever, and chest radiography is done. After she has a desaturation, she is placed on 0.5 L of O₂ by nasal cannula. Her chest radiography reveals an infiltrate consistent with pneumonia. Which best classifies her pneumonia?
 - A. Community acquired (CAP).
 - B. Hospital acquired.
 - C. Ventilator associated.
 - D. Necrotizing.

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5. A 9-year-old boy (weight 32 kg) with asthma presents to the ED with an asthma exacerbation. The patient has a history of many ED visits for his asthma and lives in a homeless shelter with his mother. After receiving three back-to-back albuterol treatments, he was initiated on every-4-hour albuterol treatments. His last treatment was 4 hours ago, and he is now doing well. Which is the best corticosteroid regimen for him?
- A. Prednisolone 60 mg orally daily for a 5-day course.
 - B. Methylprednisolone 32 mg orally three times daily for a 7-day course.
 - C. Dexamethasone 18 mg orally daily for a 2-day course.
 - D. Hydrocortisone 32 mg intramuscularly once.
6. A 4-year-old girl (weight 11 kg) was recently given a diagnosis of CF and pancreatic insufficiency. Her physician would like to initiate pancrelipase using a capsule with 6000 units of lipase/capsule. Which best describes how many capsules are needed to provide an appropriate dose with each meal?
- A. 2.
 - B. 3.
 - C. 4.
 - D. 5.
7. A 3-year-old girl presents to her pediatrician with wheezing and shortness of breath. Her mother reports that she has been given a diagnosis of asthma 1 year prior. Her mother also reports that the patient awakens coughing 1 night a month and that she had to use the albuterol inhaler she was given about three times weekly. Which is the best treatment according to the National Heart Lung and Blood Institute (NHLBI) pediatric asthma guidelines for this patient?
- A. Continue albuterol as needed for symptoms.
 - B. Add budesonide 0.5 mg nebulized daily.
 - C. Add beclomethasone hydrofluoroalkane (HFA) 80 mcg 2 puffs twice daily.
 - D. Add fluticasone 44 mcg 2 puffs twice daily.
8. A 7-year-old previously healthy boy who presents to his pediatrician with fever and cough for the past 2 days is given a diagnosis of pneumonia. His immunizations are up to date. Which is the most common cause of bacterial pneumonia in this patient?
- A. Methicillin-resistant *S. aureus* (MRSA).
 - B. *Chlamydia trachomatis*.
 - C. *H. influenzae*.
 - D. *Streptococcus pneumoniae*.
9. A 10-year-old girl (weight 27 kg) with CF presents for her regular CF clinic visit. Her home medications include the following: albuterol HFA 2 puffs inhaled twice daily; dornase alfa 2.5 mg nebulized daily; a multivitamin with extra vitamin A, D, E, and K 1 tablet orally daily; pancrelipase 12,000-unit capsules: 2 capsules with meals and 1 capsule with snacks; and fluticasone nasal spray 1 spray in each nostril daily. Her forced expiratory volume in 1 second (FEV₁) today is 81% (baseline 95%). She reports a good appetite, 2 stools/day that sink, and no abdominal pain. Which is the best treatment regimen?
- A. Continue current treatment regimen.
 - B. Increase pancrelipase 12,000-unit capsules to 3 with meals and 1 with snacks.
 - C. Add 7% hypertonic saline 4 mL inhaled twice daily.
 - D. Add fluticasone 110 mcg 2 puffs inhaled twice daily.
10. A 15-year-old male adolescent with CF has vitamin concentrations obtained at today's clinic visit. His home medications include albuterol HFA 2 puffs inhaled twice daily; dornase alfa 2.5 mg nebulized daily; pancrelipase 20,000-unit capsules 3 with meals and 2 with snacks; 7% hypertonic saline 4 mL nebulized daily; a multivitamin with extra vitamin A, D, E, K 1 tablet orally daily; and cyproheptadine 4 mg orally twice daily. Allergies include sulfa drugs – rash. The patient states that he is adherent to all of his medications. His laboratory values are as follows: 25-hydroxyvitamin D (25(OH)D) 23 ng/mL, vitamin A 33.1 mcg/dL, vitamin E 1.2 mg/dL, and INR 1.1. Which would be most appropriate to initiate?
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- A. Vitamin D3 2000 units orally daily.
 - B. Vitamin A 10,000 units orally weekly.
 - C. Vitamin E 1000 units orally daily.
 - D. Vitamin K 5 mg orally daily.
11. A 13-year-old female adolescent with asthma was admitted to the hospital for an asthma exacerbation. Her home medications include mometasone/formoterol 100/5 mcg 1 puff inhaled twice daily, albuterol HFA 2 puffs inhaled every 4 hours as needed for cough or wheezing, omeprazole 20 mg orally daily, and a multivitamin 1 tablet orally daily. The patient reports that she has been using her current controller medication for 3 months and that she occasionally misses a dose. She uses an albuterol inhaler about twice weekly and wakes up 4 or 5 days a week coughing. She has had one other hospital admission this year and three other courses of oral steroids. Which is best for the patient's controller therapy according to the Global Initiative for Asthma (GINA) guidelines?
- A. Mometasone/formoterol 200/5 mcg 1 puff inhaled twice daily.
 - B. Fluticasone 220 mcg 2 puffs inhaled twice daily.
 - C. Fluticasone/salmeterol 45/21 mcg 2 puffs inhaled twice daily.
 - D. Mometasone/formoterol 200/5 mcg 3 puffs inhaled twice daily.
12. A 5-year-old girl (weight 19 kg) with asthma is being seen in her pediatrician's office. Her current medications include albuterol HFA 2 puffs inhaled every 4 hours as needed for cough or wheezing, fluticasone 44 mcg 2 puffs inhaled twice daily, montelukast 4 mg orally daily, and a multivitamin 1 tablet orally daily. The patient's mother reports that she has not needed to use the albuterol inhaler since her last visit 6 months ago. She has had no nighttime awakenings or asthma symptoms. The patient's last course of oral corticosteroids was 2 years ago. According to the NHLBI guidelines, which inhaled controller therapy is best for this patient?
- A. Fluticasone 44 mcg 3 puffs inhaled twice daily.
 - B. Fluticasone 44 mcg 2 puffs inhaled twice daily.
 - C. Fluticasone 44 mcg 1 puff inhaled twice daily.
 - D. Fluticasone/salmeterol 230/21 mcg 2 puffs inhaled twice daily.
13. An 11-year-old girl with CF presents to her regular clinic appointment. Her current medications include albuterol HFA 2 puffs inhaled twice daily, dornase alfa 2.5 mg nebulized daily, 7% hypertonic saline 4 mL nebulized twice daily, inhaled tobramycin solution 300 mg nebulized twice daily 28 days on and 28 days off (currently an off month), and pancrelipase 12,000 unit capsules 3 capsules with meals and 2 with snacks. The patient reports increased cough and increased sputum production. Past respiratory cultures are positive for *P. aeruginosa* and MSSA. She states that she seems to feel this way every time she stops the inhaled tobramycin solution but feels well while using tobramycin inhaled. Today, her FEV₁ is 85% (baseline 97%). Which is the best treatment for this patient?
- A. Discontinue tobramycin nebulized solution, and initiate inhaled aztreonam.
 - B. Continue tobramycin nebulized solution, and add inhaled aztreonam in the off months.
 - C. Discontinue tobramycin nebulized solution, and initiate colistin inhaled and aztreonam inhaled alternating.
 - D. Continue tobramycin nebulized solution, and add inhaled vancomycin in the off months.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.9
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.4
3. Domain 3: Information Management, Research, and Education; Task(s): 3.2
4. Domain 4: Public Health and Patient Advocacy; Task(s): 4.2

I. ASTHMA

A. Background

1. In 2019, the Centers for Disease Control and Prevention reported more than 5.1 million U.S. children younger than 18 years of age were diagnosed with asthma.
2. A leading cause of ED visits, hospitalizations, and missed school days in children
3. Risk factors for asthma-related death:
 - a. Previous severe exacerbation (e.g., ICU admission, intubation/ventilation)
 - b. Two or more hospitalizations in the past year
 - c. Three or more ED visits in the past year
 - d. Hospitalization or ED visit in the past month
 - e. More than 2 canisters of a short-acting β -agonist (SABA) per month; per GINA guidelines, 12 canisters or more per year
 - f. Low socioeconomic status
 - g. Psychosocial problems
 - h. Food allergy
4. Risk factors for asthma:
 - a. Atopic disease (e.g., allergic rhinitis, eczema)
 - b. Recurrent wheezing
 - c. Parental history of asthma

B. Pathophysiology

1. Chronic inflammatory disorder of the airways that is caused by a variety of cell types (neutrophils, eosinophils, lymphocytes, mast cells) and cytokines
2. An inhaled antigen activates mast cells and T-helper 2 cells, which prompt the inflammation cascade with the production of inflammatory mediators, including histamine, leukotrienes, and cytokines. Cytokines help activate eosinophils, which migrate to the lungs. When eosinophils are activated, they release inflammatory mediators such as leukotrienes that damage airway tissue.
3. Three components
 - a. Airflow obstruction
 - b. Airway hyper-responsiveness
 - c. Inflammation
4. Airway remodeling can occur as a result of chronic inflammation.
5. Triggers
 - a. It is important to identify triggers and help patients avoid them to prevent asthma attacks.
 - b. Triggers are typically patient-specific.
 - c. Potential triggers include:
 - i. Viral respiratory tract infections
 - ii. Exercise
 - iii. Weather changes
 - iv. Exposure to tobacco smoke or other smoke
 - v. Air pollution
 - vi. Cold or hot air
 - vii. Perfumes
 - viii. Environmental allergens (e.g., dogs or cats)

C. Diagnosis

1. Signs and symptoms
 - a. Cough
 - b. Wheezing
 - c. Chest tightness
 - d. Prolonged exhalation
 - e. Shortness of breath
2. Asthma Predictive Index
 - a. Developed to aid in the diagnosis of patients younger than 3 years
 - b. High risk of asthma if three or more episodes of wheezing per year and at least one major criterion or two minor criteria
 - c. Major criteria
 - i. Eczema
 - ii. Parental asthma
 - d. Minor criteria
 - i. Allergic rhinitis
 - ii. Wheezing unrelated to colds
 - iii. Blood eosinophil count greater than 4%
3. Asthma guidelines
 - a. NHLBI guidelines
 - i. Updated in 2020
 - ii. Historically, 2007 guidelines used for pediatric asthma management
 - iii. The 2007 guidelines may still be used by some providers
 - b. GINA guidelines
 - i. Updated in 2021
 - ii. Continue to be updated
 - iii. Typically updated annually
4. NHLBI 2020 guidelines recommendation to determine initial asthma treatment
 - a. Select the appropriate table based on patient age
 - b. If patient is treatment naive, select appropriate initial therapy based on current level of asthma impairment and risk
5. GINA classification of asthma in those 6 years of age to adult
 - a. Classification is based on the step of treatment needed to control asthma symptoms.
 - b. Can be classified after having been on regular controller treatment for several months
 - c. Mild asthma: Step 1 or step 2 treatment
 - d. Moderate asthma: Step 3 treatment
 - e. Severe asthma: Step 4 or step 5 treatment

D. NHLBI Treatment

1. Treatment recommendations are listed in Tables 1–3.
2. At each visit, assess asthma control
3. If asthma not controlled
 - a. First, check adherence, inhaler technique, environmental factors, and comorbid conditions using asthma control assessments, objective measures, self-reported control, and healthcare utilization.
 - b. Not well controlled
 - i. Step up at least 1 step.
 - ii. Reevaluate in 2–6 weeks.

- c. Very poorly controlled
 - i. Short course of oral corticosteroids
 - ii. Step up 1 or 2 steps.
 - iii. Consider other diagnoses.
 - iv. Reevaluate in 2 weeks.
4. If asthma is well controlled for at least 3 months, consider a step down in therapy.
5. Peak flow meters are not routinely recommended for use in pediatric patients with asthma.

Table 1. NHLBI Treatment Steps: 0–4 Years of Age^a

	Intermittent Asthma	Persistent Asthma				
Treatment step	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Therapy recommended	SABA as needed At the start of a respiratory tract infection, add a short 7–10 d course of daily ICS	Low-dose ICS Alternative: Montelukast or cromolyn	Medium-dose ICS	Medium-dose ICS + LABA Alternative: medium dose ICS + montelukast	High-dose ICS + LABA Alternative: high-dose ICS + montelukast	High-dose ICS + LABA and oral corticosteroids Alternative: high-dose ICS + montelukast and oral corticosteroids

ICS = inhaled corticosteroids; LABA = long-acting β -agonist; NHLBI = National Heart, Lung, and Blood Institute; SABA = short-acting β -agonist.^aSABA as needed for all patients. Referral to asthma specialist recommended if need step 3 or higher and consider at step 2.**Table 2.** NHLBI Treatment Steps: 5–11 Years of Age^a

	Intermittent Asthma	Persistent Asthma				
Treatment step	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Therapy	SABA as needed	Low-dose ICS and as-needed SABA Alternative: Montelukast or theophylline or cromolyn and as-needed SABA Consider use of subcutaneous immunotherapy as adjunct therapy in individuals ≥ 5 yr	Daily and as-needed low dose ICS-formoterol Alternative: Low-dose ICS + LABA, low-dose ICS + montelukast, low-dose ICS + theophylline and as-needed SABA, or medium-dose ICS and as-needed SABA Consider use of subcutaneous immunotherapy as adjunct therapy in individuals ≥ 5 yr	Daily and as-needed medium dose ICS-formoterol Alternative: Medium-dose ICS + LABA and as-needed SABA, medium-dose ICS + montelukast, or medium-dose ICS + theophylline and as-needed SABA Consider use of subcutaneous immunotherapy as adjunct therapy in individuals ≥ 5 yr	High dose ICS + LABA + as-needed SABA Alternative: High-dose ICS + montelukast or theophylline and as-needed SABA Consider omalizumab	High-dose ICS + LABA and oral steroids and as-needed SABA Alternative: High-dose ICS + montelukast or theophylline and oral steroids and as-needed SABA Consider omalizumab

^aIf require step 4 or high, consult asthma specialist.

Table 3. NHLBI Treatment Steps: 12 Years of Age to Adult^a

	Intermittent Asthma	Persistent Asthma				
Treatment step	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Therapy	SABA as needed	Low-dose ICS and as-needed SABA or as-needed ICS and SABA combination Alternative: Cromolyn, zileuton, montelukast, or theophylline and as-needed SABA Use of subcutaneous immunotherapy recommended as adjunct	Daily and as-needed low-dose ICS-formoterol Alternative: Medium-dose ICS, low-dose ICS + LABA, low-dose ICS + LAMA, low-dose ICS + montelukast, theophylline, or zileuton and as-needed SABA Use of subcutaneous immunotherapy recommended as adjunct	Daily and as-needed medium-high dose ICS-formoterol Alternative: Medium-dose ICS-LABA, or medium-dose ICS + LAMA and as-needed SABA, medium-dose ICS + montelukast, theophylline, or zileuton and as-needed SABA Use of subcutaneous immunotherapy recommended as adjunct	Medium-high dose ICS-LABA + LAMA and as-needed SABA Alternative: Medium-high dose ICS-LABA or high-dose ICS + montelukast and as-needed SABA Consider adding asthma biologics	High-dose ICS + LABA and oral steroids and as-needed SABA Consider adding asthma biologics

LAMA = long-acting muscarinic antagonist.

^aConsult with asthma specialist if need step 4 or higher.**E. GINA Treatment**

1. For patients 5 years and younger, the following treatment steps can be considered (Table 4).
 - a. Infrequent viral wheezing and no or few interval symptoms – Step 1
 - b. Symptoms consistent with asthma, symptoms not well controlled or 3 or more exacerbations per year – Step 2
 - c. Asthma diagnosis and not well controlled on low-dose inhaled corticosteroid (ICS) – Step 3
 - d. Asthma not well controlled on a double ICS – Step 4
2. For patients 6 years and older, different steps are recommended for initial treatment on the basis of presenting symptoms (Table 5 and Table 6).
 - a. Infrequent asthma symptoms less than 2 per month – Step 1
 - b. Asthma symptoms or need for reliever medications twice or more per month – Step 2
 - c. Asthma symptoms most days of the week, or waking up at night once or more per week – Step 3
 - d. Asthma symptoms most days to daily, waking with asthma once a week or more, and low lung function – Step 4
 - e. Severely uncontrolled asthma or an acute exacerbation – short course of oral corticosteroids plus Step 5

3. If asthma not controlled (Table 7)
 - a. First, check adherence, inhaler technique, environmental factors, and comorbid conditions.
 - b. Partly controlled – Consider stepping up 1 step.
 - c. Uncontrolled
 - i. Short course of oral corticosteroids
 - ii. Step up 1 or 2 steps.
 - iii. Consider other diagnoses.
4. If asthma is well controlled for at least 3 months, consider a step down in therapy.
5. Peak flow meters are not routinely recommended for use in pediatric patients with asthma.

Table 4. GINA Treatment Steps: ≤5 Years of Age^a

	Step 1	Step 2	Step 3	Step 4
Preferred controller	SABA as needed	Low-dose ICS	Double low-dose ICS	Continue controller and refer to specialist
Alternatives		Montelukast or short course of ICS with onset of respiratory illness	Low-dose ICS + montelukast Consider specialist referral	Add montelukast Consider specialist referral Increase ICS frequency; add intermittent ICS when SABA taken

^aPreferred reliever medication: SABA as needed.**Table 5.** GINA Treatment Steps: 6–11 Years of Age^a

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller	Low-dose ICS taken whenever SABA is taken	Low-dose ICS	Low-dose ICS/LABA, medium-dose ICS, or very low-dose ICS-formoterol daily and as needed (MART)	Medium-dose ICS-LABA or low-dose ICS-formoterol daily and as needed (MART) and refer to specialist	Refer for phenotypic assessment ± add-on therapy higher-dose ICS-LABA (e.g., anti-IgE)
Alternatives	Low-dose ICS and SABA as needed	Montelukast or low-dose ICS taken whenever SABA is taken	Low-dose ICS + montelukast Consider specialist referral	Add tiotropium or montelukast Consider specialist referral	Add on anti-IL-5 or low-dose oral corticosteroid

IgE = immunoglobulin E; IL = interleukin; MART = maintenance and reliever.

^aPreferred reliever medication: SABA as needed (or-ICS-formoterol reliever for MART therapy).

Table 6. GINA Treatment Steps: 12 Years of Age to Adult^a

	Step 1	Step 2	Step 3	Step 4	Step 5
Preferred controller	As-needed low-dose ICS/formoterol	As-needed low-dose ICS/formoterol	Low-dose maintenance ICS/formoterol	Medium-dose maintenance ICS/formoterol	High-dose ICS/formoterol + LAMA Refer for phenotypic assessment ± add-on therapy (biologic agents)
Alternatives	Low-dose ICS taken whenever SABA is taken	Low-dose ICS taken whenever SABA is taken or montelukast	Low-dose ICS + LABA, medium-dose ICS, or add on montelukast	Medium/high-dose ICS + LABA, add on LAMA, add on montelukast, or switch to high-dose ICS	Add on LAMA, add low-dose oral corticosteroid, montelukast, or azithromycin (adults)

^aPreferred reliever medication: As-needed low-dose ICS/formoterol (steps 1 and 2). Alternative reliever is a SABA as needed.

Table 7. GINA Assessing Asthma Control: 6 Yr to Adult^a

	Well Controlled	Partly Controlled	Uncontrolled
Daytime asthma symptoms more than twice/week?	None of these	1 or 2	3 or 4
Any night waking because of asthma?			
Disturbance of normal activity?			
SABA use more than twice per week?			

^aConsider other risk factors for exacerbations, including number of past exacerbations.

F. Medications

1. SABAs

- a. Mechanism of action
 - i. SABAs bind to β_2 -receptors on airway smooth muscle.
 - ii. Signals a cascade, causing smooth muscle relaxation
- b. Adverse effects
 - i. Agitation
 - ii. Irritability
 - iii. Tachycardia
 - iv. Tremor
 - v. Hypokalemia
 - vi. Hyperglycemia
- c. Drugs and dosage forms:
 - i. Albuterol: Typically dosed every 4 hours as needed
 - (a) Nebulization solution (1.25 mg/3 mL, 2.5 mg/3 mL, 5 mg/1 mL)
 - (b) Metered dose inhaler (MDI) 90 mcg/puff
 - (c) Breath-actuated dry powder inhaler (DPI) for respiclick and digihaler
 - ii. Levalbuterol: Typically dosed every 4 hours as needed
 - (a) Nebulizer solution (0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL)
 - (b) MDI 45 mcg/puff
 - (c) Levalbuterol 1.25 mg = albuterol 2.5 mg.
 - (d) Does not confer additional benefits over albuterol

2. ICSs

- a. Preferred therapy for long-term control in children
- b. Mechanism of action: Anti-inflammatory activity
- c. Controller medication counseling tips
 - i. Take every day when well or sick.
 - ii. Onset of action takes a few days.
 - iii. Response increases over several weeks to months to maximal (max) effect.
 - iv. Rinse mouth or brush teeth after use to prevent thrush.
 - v. Use MDI with spacer.
- d. Adverse effects
 - i. Linear growth velocity was reduced by around 1 cm in the first year of treatment with a low- to medium-dose ICS; however, the patients' height reached that of patients without ICS use a few years later.
 - ii. Adverse effects are generally low because systemic absorption is low.
 - iii. Thrush
- e. ICS doses by age and steroid (Table 8)

Table 8. ICS Strengths by Steroid and Age per GINA/NHLBI Guidelines^a

	0–5 Years-Old	6–11-Years-Old	12 Years of Age and Older
Budesonide (nebulized)	Low: 500	Low: 250–500 Medium: >500–1000 High: >1000	---
Budesonide (DPI)	---	Low: 100–200 Medium: >200–400 High: >400	Low: 200–400 Medium: >400–800 High: >800
Beclometasone (standard particle MDI)	Low: 100	Low: 100–200 Medium: >200–400 High: >400	Low: 200–500 Medium: >500–1000 High: >1000
Beclometasone (extra-fine particle MDI)	Low: 50	Low: 50–100 Medium: >100–200 High: >200	Low: 100–200 Medium: >200–400 High: >400
Fluticasone propionate (MDI)	Low: 50	Low: 50–100 Medium: >100–200 High: >200	Low: 100–250 Medium: >250–500 High: > 500
Fluticasone propionate (DPI)	---	Low: 50–100 Medium: >100–200 High: >200	Low: 100–250 Medium: >250–500 High: > 500
Fluticasone furoate (DPI)	---	Low: 50 Medium: 50	Low: 100 Medium: 100 High: 200
Mometasone (MDI)	Low: 100	Low: 100 Medium: 100 High: 200	Low: 200–400 Medium: 200–400 High: > 400
Mometasone (DPI)	---	---	Low: 200 Medium: 200 High: 400
Ciclesonide (HFA)	---	Low: 80 Medium: >80–160 High: >160	Low: 80–160 Medium: >160–320 High: >320

DPI = dry powder inhaler; HFA = hydrofluoroalkane; MDI = metered dose inhaler.

^a All doses listed in mcg.

3. ICS plus a long-acting β -agonist (LABA)
 - a. Mechanism of action
 - i. The ICS component decreases airway inflammation.
 - ii. LABA – Binds to β_2 -receptors and provides bronchodilation
 - b. Adverse effects – Similar to SABA and ICS adverse effects
 - c. Monotherapy with a LABA is not recommended in asthma.
 - i. Masks airway inflammation
 - ii. Risk of sudden and life-threatening asthma exacerbations
 - iii. Use in combination with an ICS.
 - d. Data analyses for an ICS plus a LABA in pediatric patients
 - i. Adult data analyses show that adding a LABA to an ICS improves asthma control.
 - ii. Efficacy data in young children are lacking.
 - iii. Carefully monitor young patients taking an ICS plus a LABA.
 - e. GINA guidelines recommend low-dose ICS/formoterol as needed as reliever medication for patients 6 years and older; per the NHLBI guidelines, use of this can be done down to 4 years of age (see tables for details on which steps)
 - i. All data with budesonide/formoterol
 - ii. Avoids SABA-only treatment, which has proven less effective
 - iii. Decreased exacerbations and increased number of weeks asthma controlled over SABA alone
 - f. Drugs and dosage forms
 - i. Fluticasone/salmeterol
 - (a) MDI (dosing 2 puffs twice daily): 45/21 mcg/puff, 115/21 mcg/puff, 230/21 mcg/puff
 - (b) DPI (dosing 1 puff twice daily): 100/50 mcg/inhalation, 250/50 mcg/inhalation, 500/50 mcg/inhalation
 - (c) Inhalation powder (dosing 1 puff twice daily): 55/14 mcg/inhalation, 113/14 mcg/inhalation, 232/14 mcg/inhalation
 - ii. Budesonide/formoterol: MDI (dosing 2 puffs twice daily): 80/4.5 mcg/puff, 160/4.5 mcg/puff
 - iii. Mometasone/formoterol: MDI (dosing 2 puffs twice daily): 100/5 mcg/puff, 200/5 mcg/puff
 - iv. Fluticasone furoate/vilanterol: DPI (dosing 1 puff daily): 100/25 mcg/puff, 200/25 mcg/puff
4. Leukotriene antagonists
 - a. Generally a well-tolerated oral option, which may improve adherence
 - b. Mechanism of action: Block leukotrienes, which are part of the inflammatory pathway
 - c. Adverse effects
 - i. Usually well tolerated
 - ii. Sedation
 - iii. Black box warning for neuropsychiatric events including suicidal ideation
 - d. Drugs and dosage forms
 - i. Montelukast (Singulair)
 - (a) 1–5 years: 4 mg orally daily
 - (b) 6–14 years: 5 mg orally daily
 - (c) 15 years and older: 10 mg orally daily
 - (d) Dosage forms: Oral granule packet: 4 mg; chewable tablet: 4 mg, 5 mg; tablet: 10 mg
 - ii. Zafirlukast (Accolate)
 - (a) 5–11 years: 10 mg orally twice daily
 - (b) 12 years and older: 20 mg orally twice daily
 - (c) Dosage forms: Tablet: 10 mg, 20 mg
 - iii. Zileuton (Zyflo; 5-lipoxygenase inhibitor)
 - (a) Mechanism of action: Inhibits leukotriene formation by inhibiting 5-lipoxygenase

- (b) Adverse effects
 - (1) Liver toxicity
 - (2) Leukopenia
 - (3) Abdominal pain
 - (c) Dosage forms: Tablet: 600 mg; extended-release tablet: 600 mg
 - (d) Dosing
 - (1) Immediate release for children 12 years and older – 600 mg orally four times daily
 - (2) Extended release for children 12 years and older – 1200 mg orally twice daily
- 5. Tiotropium (Spiriva Respimat)
 - a. Bronchodilator, long-acting muscarinic antagonist
 - b. Indicated: Maintenance therapy in patients 6 years and older (FDA approval); according to the guidelines, not recommended in those younger than 12 years. Added to other treatment in patients with a history of exacerbations
 - c. Dose: 2 inhalations/day (1.25 mcg/puff)
 - d. Adverse effects
 - i. Urinary retention
 - ii. Worsening narrow-angle glaucoma
 - iii. Bronchospasm
 - e. Administration: Inhaled by the accompanying device, instruction recommended
- 6. Omalizumab (Xolair)
 - a. Anti-immunoglobulin E (IgE) monoclonal antibody
 - b. Indicated: Moderate to severe persistent asthma in patients older than 6 years with positive allergic skin test not controlled with ICSs
 - c. Doses of 75–375 mg every 2–4 weeks; dose on the basis of age, weight, and pretreatment IgE concentrations
 - d. Adverse effects: Anaphylaxis, bronchospasm, hypotension, urticaria, angioedema, serum sickness
 - e. Administration of first three subcutaneous injections in a clinic or medical facility is necessary for monitoring, then can consider self-administration. Intramuscular epinephrine should be available for 24 hours after dose administration.
 - f. Dosage forms: Prefilled syringe 75 mg/0.5 mL and 150 mg/1 mL; solution for reconstitution 150 mg
- 7. Mepolizumab (Nucala)
 - a. Anti-interleukin(IL)-5
 - b. Indicated: Patients 6 years and older with severe asthma and eosinophilic phenotype as add-on chronic therapy
 - c. Dose: Age 12 years and older: 100 mg subcutaneously every 4 weeks; age 6–11 years: 40 mg subcutaneously every 4 weeks
 - d. Adverse effects: Hypersensitivity reaction, herpes zoster infection – Consider varicella vaccination before use, headache, injection-site reaction
 - e. Can be administered by a medical professional; or can self-administer (auto-injector, prefilled syringe)
 - f. Dosage forms: Auto-injector 100 mg/1 mL; prefilled syringe 100 mL/1 mL; solution for reconstitution 100 mg
- 8. Dupilumab (Dupixent)
 - a. Anti-IL-4 and blocks both IL-4 and IL-13
 - b. Indicated: Patients 6 years and older with eosinophilic phenotype or oral corticosteroid-dependent asthma as add-on therapy

- c. Dose: 12 years of age or older: Initial dose 400 mg subcutaneously, then 200 mg given every other week; If also receiving oral corticosteroids or have comorbidity of moderate to severe atopic dermatitis, use initial dose of 600 mg subcutaneously, then 300 mg given every other week; 6–11 years of age: 15 to less than 30 kg: 100 mg every other week or 300 mg every four weeks; 30 kg or more: 200 mg every other week
 - d. Adverse effects: Hypersensitivity reaction, conjunctivitis, keratitis, rash, oropharyngeal pain, neuropathy, eosinophilia
 - e. Can self-administer
 - f. Treat parasitic infections before starting treatment and avoid use of live vaccines.
9. Reslizumab (Cinqair)
- a. IL-5 antagonist
 - b. Indicated: 18 years and older as add-on treatment for severe asthma with eosinophilic phenotype
 - c. Dose: 3 mg/kg intravenously every 4 weeks
 - d. Adverse effects: Increased creatine phosphokinase, myalgia, oropharyngeal pain, anaphylaxis
 - e. Observe after infusion for reaction.
10. Benralizumab (Fasenra)
- a. Binds to IL-5 receptor on eosinophils to facilitate eosinophil death
 - b. Indicated: Patients 12 years and older with severe asthma and eosinophilic phenotype as add-on chronic therapy
 - c. Dose: 30 mg subcutaneously every 4 weeks for the first three doses, followed by once every 8 weeks thereafter
 - d. Adverse effects: Hypersensitivity reaction, headache, and pharyngitis
 - e. Can be administered by a medical professional or if using auto-injector, can consider home administration

Patient Case

Questions 1 and 2 pertain to the following case.

M.B. is a 6-year-old girl who presents to the primary care provider with difficulty breathing and wheezing. Her mother reports that once a week, she wakes up at night coughing. In addition, she sometimes struggles to keep up with her friends and often has to stop while playing. She is currently taking albuterol 2 puffs inhaled every 4 hours as needed for cough or wheezing.

1. When assessing M.B.'s asthma control, which of the following is important to consider?
 - A. Height.
 - B. Inhaler technique.
 - C. Family history.
 - D. Inhaler color.
2. Which is the best medication regimen for M.B. according to the NHLBI guidelines?
 - A. Budesonide DPI 180 mcg 2 puffs inhaled twice daily and albuterol 2.5 mg nebulized every 4 hours as needed for cough or wheezing.
 - B. Fluticasone HFA 44 mcg 1 puff inhaled twice daily and albuterol HFA 2 puffs inhaled every 4 hours as needed for cough or wheezing.
 - C. Beclomethasone HFA 80 mcg 2 puffs inhaled twice daily and albuterol 2.5 mg nebulized every 4 hours as needed for cough or wheezing.
 - D. Budesonide 1 mg nebulized twice daily and albuterol HFA 2 puffs inhaled every 4 hours as needed for cough or wheezing.

G. Medication Use in Children

1. Appropriate technique is important for administering inhaled medications to children.
2. Inhaler technique should be assessed at appointments to ensure adequate delivery.
3. Nebulizers
 - a. Should be administered using a mask for younger patients or a mouthpiece if children can consistently breathe through their mouth
 - b. Blow-by administration of nebulized medications is not recommended because this reduces the amount of medication the patient inhales.
4. MDI
 - a. MDIs can be used in a patient at any age with the use of a spacer.
 - b. Recommended by the GINA guidelines for children 0–5 years of age with a spacer/valved holding chamber device
 - c. Use of a spacer/valved holding chamber device is recommended to increase medication delivery to the lungs.
 - d. Spacer versus valved holding chamber
 - i. Spacer – Creates a space between the mouth and the medication to help with administration but does not have a one-way valve
 - ii. Valved holding chamber – Has a one-way valve at the mouthpiece that gives the patient time to take a slow, deep breath and prevents exhaling into the tube
 - iii. Most patients will use these two terms interchangeably.
 - iv. Prefer to use a valved holding chamber – This will be called a spacer for the rest of the text.
 - e. Spacer with a mask
 - i. Recommended for children younger than 5 years or for patients who cannot follow directions to take a deep breath and hold
 - ii. Directions for use:
 - (a) Shake the inhaler and remove the cap.
 - (b) Place the inhaler into the backside of the spacer.
 - (c) Place the mask around the child's nose and mouth, making a good seal.
 - (d) Spray 1 puff into the spacer, and let the child take 5 or 6 normal breaths.
 - (e) If more than 1 puff is required, wait about 1 minute and then repeat steps c and d for the next puff.
 - f. Spacer with a mouthpiece
 - i. Recommended for children older than 5 years who can follow directions to take a deep breath and hold
 - ii. Directions for use:
 - (a) Shake the inhaler and remove the cap.
 - (b) Place the inhaler into the backside of the spacer.
 - (c) Place the mouthpiece in the child's mouth so that his or her lips make a good seal around the mouthpiece and the tongue does not cover the opening.
 - (d) Spray 1 puff into the spacer, and have children take a slow deep breath and hold it for 5 seconds.
 - (e) If more than 1 puff is required, wait about 1 minute and then repeat steps c and d for the next puff.
5. DPI
 - a. Technique differs from MDI technique.
 - b. DPIs require a more forceful inhalation to mobilize the dry powder into the lungs.
 - c. DPI technique can be difficult for children to consistently perform correctly.
 - d. DPIs should not be used in children unless the child can consistently demonstrate the correct technique.

H. Asthma Action Plan

1. A written care plan for asthma treatment personalized for the patient
2. Asthma triggers should be documented so that the patient can try to avoid them.
3. The plan can be used as an educational tool as well as a guide for symptom management for the family.
4. The asthma action plan should be shared with the school or day care.
5. The plan has three zones: Green, yellow, red
 - a. Green – Patients follow when they are doing well; contains information on controller medications
 - b. Yellow – Patients use when their asthma is getting worse; contains instructions on how to modify their medications for these symptoms (e.g., use of SABA, intermittent use of ICS-formoterol)
 - c. Red – Patients use when very short of breath and yellow-zone management has not worked; contains directions on how to use the as-needed medications like SABA and may include starting oral corticosteroids, as well as the person(s) to call for additional help

I. Pharmacogenomics and Asthma

1. Pharmacogenomic variants may affect the efficacy of many common asthma medications.
2. SABA
 - a. Response is determined genetically.
 - b. *ADRB2* gene – Variant Arg16Gly
 - c. *THRB* gene – Variant rs892940
 - d. *ASB3/SOCS* gene – Several variants
 - e. *SPATA13-AS1* gene
 - f. *SLC22A15* gene
3. LABAs
 - a. *ADRB2* gene – Variant Arg16Gly, Ile164, -376ins
 - b. *HSP8A* gene
4. ICSs – Genes thought to be involved in patient response: *CHRM2*, *ZNF432*, *CYP3A4*, *GLCCII*, *FBXL7*, *CA10*, *SGK493*, *CTNNA3*, *CRISPLD2*, *SPATA20*, *ACOT4*, *BRWD1*, *ALG8*, *NAPRTI*
5. Glucocorticoids/corticosteroids – Genes thought to be involved in patient response: *HDAC1*, *CRHR1*
6. Leukotriene modifiers – Genes thought to be involved in patient response: *MRPP3*, *GLT1D1*, *COL2A1*
7. This is a changing and evolving part of asthma care.

Patient Case

3. A 10-year-old boy with asthma is admitted to the hospital for acute shortness of breath and cough. His home medications include fluticasone HFA 44 mcg 1 puff inhaled twice daily, albuterol 2.5 mg nebulized every 4 hours as needed for cough or wheezing, and a chewable multivitamin 1 tablet orally daily. He is being treated for an asthma exacerbation. His mother reports that he misses taking his fluticasone dose twice monthly and that he uses albuterol about three times weekly, has symptoms during the day four times per week, and has 2 nighttime awakenings per month. Review of use of inhaler and spacer was confirmed and appropriate. Which is the optimal home treatment regimen according to the GINA guidelines?
 - A. Fluticasone HFA 44 mcg 1 puff inhaled twice daily.
 - B. Fluticasone HFA 110 mcg 1 puff inhaled twice daily.
 - C. Fluticasone/salmeterol HFA 115/21 mcg 2 puffs inhaled twice daily.
 - D. Fluticasone/salmeterol HFA 230/21 mcg 2 puffs inhaled twice daily.

II. STATUS ASTHMATICUS

- A. Background
 1. One of the top indications for ICU admission for children
 2. Risk factors for life-threatening deterioration
 - a. History of a life-threatening exacerbation (ICU admission, intubation)
 - b. Older age
 - c. Inability to recognize airflow obstructions
 - d. Poor asthma control
 3. Early recognition and treatment of an asthma exacerbation is the best management.
- B. Pathophysiology: Bronchial smooth muscle spasm, airway inflammation, and increased mucus production are all components of an acute asthma exacerbation.
- C. Assessment and Treatment (Table 9)
 1. Signs and symptoms
 - a. Shortness of breath
 - b. Increased work of breathing/use of accessory muscles
 - c. Diminished or absent breath sounds
 - d. Wheezing
 - e. Decreased ability to speak or count
 - f. Anxiety

Table 9. Classifying the Exacerbation

Exacerbation	Signs and Symptoms	FEV ₁ (%)	Treatment
Mild	Dyspnea or tachypnea with activity • Can lie down • Increased respiratory rate • End-expiratory wheezing	> 70	• Treat at home using a SABA • Consider a course of oral corticosteroids
Moderate	Dyspnea/tachypnea interferes with normal activity • Prefers sitting • Shorter cry • Difficulty feeding • Talks in phrases • Increased respiratory rate • Uses accessory muscles to breath • Loud wheezing • Heart rate elevated	40–69	• Office or ED visit • Use a SABA • Oral corticosteroids

Table 9. Classifying the Exacerbation (*continued*)

Exacerbation	Signs and Symptoms	FEV ₁ (%)	Treatment
Severe	Dyspnea/tachypnea at rest • Sits upright • Can only say single words • Increased respiratory rate • Use of accessory muscles • Loud wheezing in inhalation and exhalation • Heart rate elevated	< 40	• ED visit and possibly hospitalization • Use a SABA • Oral or IV corticosteroids
Life threatening	Too dyspneic to speak; perspiring	< 25	• ED visit/ICU • Use a SABA • IV corticosteroids

IV = intravenous(ly).

2. Home management: Inhaled SABA up to two treatments 20 minutes apart
 - a. Good response (FEV₁ of 80% or greater): Continue SABA every 4 hours for 24–48 hours; consider short course of oral corticosteroids.
 - b. Incomplete response (FEV₁ of 50%–79%): SABA every 4 hours, oral corticosteroids; contact physician for follow-up instructions
 - c. Poor response (FEV₁ less than 50%): Repeat SABA immediately, oral corticosteroids; if severe distress, go to the ED
3. Hospital/ED management
 - a. Initial assessment and provide supplemental oxygen (maintain SaO₂ greater than 90%), if necessary
 - b. First-line treatments
 - i. Inhaled bronchodilators
 - (a) Mild to moderate exacerbations: SABA up to three doses in first hour
 - (b) Severe exacerbations: SABA plus ipratropium every 20 minutes or continuously for 1 hour
 - (c) After the initial treatment, the patient is assessed, and albuterol is continued at the frequency the patient requires: Continuous albuterol, every 2 hours, every 3 hours, every 4 hours, etc.
 - (d) SABA dose and frequency are weaned depending on patient symptoms or asthma scoring system.
 - ii. Systemic corticosteroids
 - (a) Used to treat airway inflammation
 - (b) Early administration is key.
 - (c) Prednisone, methylprednisolone, or prednisolone: 1–2 mg/kg/day in a daily or divided dose (max 60 mg/day) according to GINA guidelines; max 40 mg/day
 - (d) Prednisolone is preferred when oral liquid is required because of its palatability.
 - (e) In severe exacerbations, intravenous corticosteroids may be considered because of potential changes in GI tract perfusion. Methylprednisolone 1–2 mg/kg/day divided every 6–12 hours (max 60 mg/day)
 - (f) Duration of oral corticosteroids is variable, and the recommended course is 3–10 days.
 - (g) Dexamethasone in the ED
 - (1) Prednisolone and prednisone are the most-studied oral corticosteroids in pediatric asthma.
 - (2) Up to 28% of patients do not fill their corticosteroid prescription.

- (3) An unknown number of patients do not complete their corticosteroid course.
- (4) Early supplemental treatments (ED management)
- (5) Dexamethasone has been proposed as a steroid option, given its longer half-life.
- (6) A meta-analysis concluded that, in comparing a one- or two-dose dexamethasone regimen with a 5-day prednisolone regimen, relapse rate did not differ, but patient vomiting was less in those with asthma exacerbations discharged from the ED on dexamethasone. However, the studies included in the meta-analysis varied with respect to the dexamethasone dose and equivalent dosing of prednisolone/prednisone.
- (7) Dexamethasone administered orally or intramuscularly 0.6 mg/kg/dose (max dose 16–18 mg) every 24 hours - 1 or 2 doses is an option for status asthmaticus treatment in the ED.
- iii. Ipratropium nebulized
 - (a) Anticholinergic bronchodilator
 - (b) Recommended for use in the ED – Reduces hospitalizations
 - (c) Not recommended beyond initial period
 - (d) Dose: Ipratropium 0.25–0.5 mg for three doses back to back and then up to every 6 hours as needed (typically 0.5 mg)
- iv. Intravenous magnesium sulfate
 - (a) Smooth muscle relaxation, decreases cholinergic stimulation and histamine release = bronchodilation
 - (b) Dose: 25–75 mg/kg (max 2000 mg) over 20 minutes
 - (c) Adverse effects: Weakness, respiratory depression, cardiac arrhythmias
- v. Helium-oxygen (heliox)
 - (a) Lower density and higher viscosity than air
 - (b) Flows more easily through small and obstructed airways in patients with asthma
 - (c) Expensive
 - (d) Literature conflicting regarding efficacy
- c. Other treatment options to avoid intubation
 - i. Pharmacologic treatments
 - (a) Terbutaline intravenously
 - (1) β -Adrenergic agonist
 - (2) Causes bronchodilation
 - (3) Improves gas exchange and shortens hospital and ICU length of stay
 - (4) In a placebo-controlled trial, did not have increased efficacy over standard of care
 - (5) Adverse effects: Tachyarrhythmias, hypertension, electrolyte disturbances, nausea, vomiting, and agitation
 - (6) Can be used after failure of continuous nebulization of SABAs
 - (b) Aminophylline intravenously
 - (1) Methylxanthine, bronchodilator
 - (2) Intravenous infusion requires drug concentration monitoring, given its narrow therapeutic index.
 - (3) Adverse effects: Nausea, vomiting, headache, tremor, arrhythmias
 - (4) Can be used after failure of continuous nebulization of SABAs
 - (5) Therapeutic concentrations: 5–15 mcg/mL
 - (c) Ketamine
 - (1) Anesthetic with sympathomimetic and bronchodilator properties
 - (2) Can increase bronchial secretions
 - (3) Intravenous

- (4) Emergence phenomenon may be frightening.
 - (5) Last-line option to prevent intubation – Case reports
 - (6) Option for mechanically ventilated patients
 - ii. Nonpharmacologic treatments
 - (a) Noninvasive positive pressure ventilation
 - (1) Used to prevent airway collapse during exhalation
 - (2) Should be closely observed with this treatment
 - (b) Intubation
 - (1) A last resort
 - (2) Other treatments with few efficacy data are used to try to avoid the need for intubation.
 - (3) Intubation can aggravate bronchospasm, and gas exchange can in fact be worse postintubation.
 - (4) Should be done by experienced clinician
 - (5) Can be difficult to manage
- d. Discharge
 - i. Patients should be weaned on a SABA to at least every 3- to 4-hour treatments.
 - ii. Assess the asthma control of patients to determine whether changes to their maintenance therapy are needed.
 - iii. Asthma education is important for families and older patients.

Patient Cases

4. A 3-year-old girl (weight 12 kg) presents to the ED with increased work of breathing, retractions, and decreased breath sounds. Her medical history is significant for GERD (gastroesophageal reflux disease) and asthma. She was placed on oxygen and is currently receiving three back-to-back treatments of albuterol/ipratropium. She is responding to the albuterol/ipratropium treatments. Which treatment would be best to administer next?
 - A. Magnesium 600 mg intravenously once.
 - B. Aminophylline continuous infusion.
 - C. Prednisolone 24 mg orally daily.
 - D. Methylprednisolone 1 mg intravenously every 6 hours.
5. An 11-year-old boy (weight 43 kg) with asthma who presented with increased work of breathing and loud wheezing is currently in the pediatric ICU receiving continuous albuterol 20 mg/hour and methylprednisolone 15 mg intravenously every 6 hours; he has received one magnesium bolus. The patient continues to have a respiratory rate of 29 breaths/minute and an increased oxygen requirement on 3 L of non-rebreather facemask. Which is the best treatment for this patient?
 - A. Terbutaline continuous infusion intravenously.
 - B. Ketamine continuous infusion intravenously.
 - C. Fluticasone inhaled.
 - D. Epinephrine subcutaneously.

III. CYSTIC FIBROSIS

A. Background

1. Most common lethal genetic disease in Caucasian populations
2. Incidence: 1 in every 3000
3. Inheritance type: Autosomal recessive
4. Median life expectancy: 47 years
5. In 2012, almost one-half of all patients with CF were older than 18 years.

B. Pathophysiology

1. Caused by a mutation in the gene that encodes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein
2. More than 1800 CFTR mutations have been identified.
3. CFTR
 - a. CFTR functions as a chloride channel.
 - b. CFTR is located in many areas of the body (e.g., lungs, GI tract, liver).
 - c. CFTR dysfunction hinders exocrine function.
 - d. Non-CF lung (Figure 1)
 - i. CFTR channel allows chloride transport.
 - ii. In the airway, an equilibrium is established between chloride, sodium, and water.
 - iii. Airway mucus is well hydrated and easily cleared by cilia.
 - e. CF lung (Figure 2)
 - i. CFTR channel is absent or function is reduced.
 - ii. Chloride, which is not transported out of the epithelial cell, creates a disequilibrium with sodium and water.
 - iii. Sodium is drawn back into the cell, and water follows.
 - iv. Results in dehydrated mucus that makes a good environment for bacteria and does not clear from airway
 - v. DNA and immune cells also become trapped in the mucus.

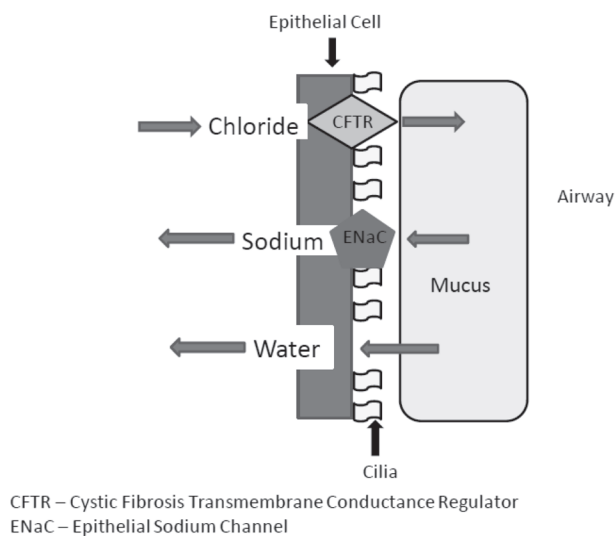


Figure 1. Non-cystic fibrosis lung.

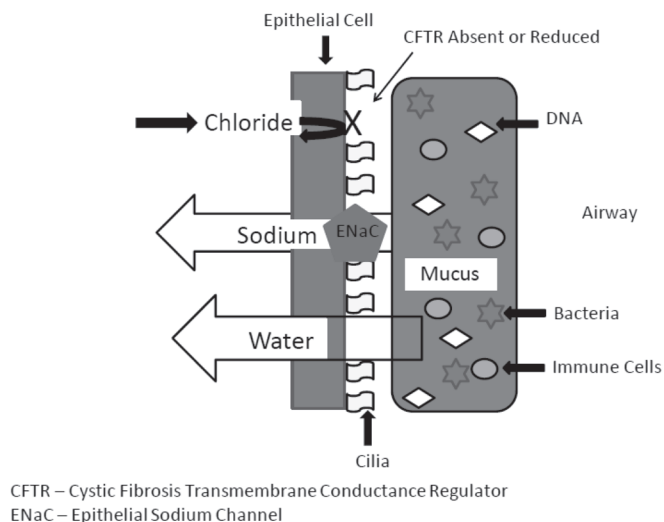


Figure 2. Cystic fibrosis lung.

4. Multiorgan disease – Including lung, liver, pancreas, and GI tract
5. *CFTR* mutation classes
 - a. *CFTR* mutations are currently categorized into six classes.
 - b. *CFTR* genotype is not directly correlated with clinical phenotype.
 - c. Class I – No CFTR at cell membrane
 - i. Premature stop codon
 - ii. Messenger RNA translation discontinued
 - iii. About 10% of patients with CF
 - iv. For example, G542X
 - d. Class II – Little to no CFTR reaches membrane.
 - i. Trafficking/folding defect
 - ii. Most common
 - iii. About 80% of patients with CF
 - iv. For example, F508del
 - e. Class III – CFTR reaches membrane but does not work.
 - i. Gating mutations
 - ii. About 5% of patients with CF
 - iii. For example, G551D
 - f. Class IV – CFTR reaches membrane and has some function.
 - i. Channel narrowing
 - ii. Less than 2% of patients with CF
 - iii. For example, R334W
 - g. Class V – Small amount of functional CFTR reaches cell membrane.
 - i. Splicing defect
 - ii. Less than 2% of patients with CF
 - iii. For example, 3120+1G→A
 - h. Class VI – CFTR reaches membrane but fast turnover
 - i. C-terminus mutations
 - ii. Less than 2% of patients with CF
 - iii. For example, 1811 + 1.6 kbA→G

C. Diagnosis

1. Newborn screening for CF
 - a. Active in all 50 U.S. states and in many countries across the world
 - b. Earlier diagnosis and treatment of CF have increased patient weight and decreased hospitalizations.
 - c. Newborn screening programs vary by state and country. States differ on which tests are used and in what order they are performed.
 - d. Newborn screening will miss some individuals with CF – Patients without pancreatic involvement
 - e. IRT (immunoreactive trypsinogen)
 - i. High value equals positive newborn screen.
 - ii. Not diagnostic for CF
 - iii. Further testing is needed to confirm diagnosis.
 - f. CFTR DNA sequencing
 - i. Blood spot is used to run a panel of common CF mutations for the area.
 - ii. Patients can be identified as having one or two disease-causing mutations.
 - g. Sweat test
 - i. Gold standard diagnostic tool
 - ii. Must be done at an accredited laboratory
 - iii. Pilocarpine iontophoresis
 - iv. 60 mEq/L or greater: Diagnostic
 - v. Intermediate: 30–59 mEq/L
2. Clinical diagnosis of CF
 - a. Signs and symptoms: Steatorrhea, failure to thrive, recurrent sinopulmonary infections, rectal prolapse, meconium ileus, salt depletion syndrome, family history
 - b. If clinically suggestive of CF, a sweat test should be performed.
3. Diagnosis of pancreatic insufficiency
 - a. Symptoms include increased stool frequency, fatty stools, and failure to thrive.
 - b. Fecal elastase
 - i. Quantifies human fecal elastase, so pancreatic enzymes do not affect the test results
 - ii. Should be checked in infants with CF
 - iii. If concentration is 50–200 mcg/g – Pancreatic insufficient: Treat with pancreatic enzymes.
 - iv. Greater than 200 mcg/g – Pancreatic sufficient, though could become pancreatic insufficient over time

D. Lung Disease

1. Cause of around 85% of CF deaths
2. Cycle: Thick mucus → infection → inflammation → tissue damage
3. Chronic treatments
4. Many different bacteria can colonize the lungs of patients with CF, including MSSA, *H. influenzae*, MRSA, and *P. aeruginosa*.
5. Chronic medications/treatments for lung health
 - a. Airway clearance therapy
 - i. Recommended for all patients with CF
 - ii. Used to help move mucus out of the lungs
 - iii. Typically used regularly twice daily and at increased frequency during exacerbations
 - iv. No method has been proven better than another.
 - v. Options include
 - (a) Percussion and postural drainage
 - (b) Positive expiratory pressure
 - (c) Active cycle of breathing

- (d) High-frequency chest compression
- (e) Autogenic drainage
- (f) Oscillatory PEP (positive expiratory pressure)
- (g) Exercise
- b. Dornase alfa
 - i. Cleaves extracellular DNA from neutrophils and other inflammatory cells in the CF mucus
 - ii. Reduces mucus viscosity
 - iii. Dose: 2.5 mg nebulized daily is recommended in patients 6 years and older with CF; in patients 2–5 years, can be offered selectively on an individual clinical basis
 - iv. Generally well tolerated; voice alterations have occurred
 - v. Increasing to twice-daily dosing may be indicated in patients older than 21 years or with a forced vital capacity (FVC) greater than 85%, on a chronic basis. Increases to twice daily in other patients are not effective.
- c. 7% hypertonic saline
 - i. Exact mechanism unclear – Proposed that sodium chloride creates an osmotic gradient, drawing water into the airway to increase airway surface liquid
 - ii. Recommended for patients with CF who are 6 years and older; in patients 2–5 years of age, can be offered selectively on an individual clinical basis
 - iii. Safety of 7% hypertonic saline has been established in patients younger than 6 years; however, efficacy has not been established in this age group.
 - iv. Dose: 4 mL nebulized twice daily
 - v. Adverse effects: Bronchospasm (pretreat with albuterol), throat irritation
 - vi. Also available as 3% and 3.5% concentrations for patients unable to tolerate 7%
- d. Azithromycin
 - i. Exact mechanism unclear – Immunomodulating effects and effects on *Pseudomonas* bio-film formation
 - ii. Recommended for use in patients with CF who are 6 years and older with persistent *P. aeruginosa* to improve lung function and reduce exacerbations
 - iii. Consider using to reduce exacerbations in patients with CF without persistent *P. aeruginosa* who are 6 years and older.
 - iv. No recommendation for or against in age 2–5 years
 - v. Was studied in patients 6 months to 18 years of age as addition to inhaled tobramycin for *Pseudomonas* eradication; azithromycin was continued for 18 months and decreased exacerbation but made no difference in *Pseudomonas* eradication rate
 - vi. Azithromycin 250 mg three times weekly for weight less than 36–40 kg; azithromycin 500 mg three times weekly for weight greater than 36–40 kg
 - vii. Adverse effects: GI intolerance, concern for increased resistance in patients with occult or active nontuberculous mycobacteria (NTM) infection, QTc prolongation when given concurrently with other QTc-prolonging agents
 - viii. Monitoring: Screen for NTM infection before starting and then every 6–12 months.
 - ix. Not recommended for patients with NTM infection
- e. Inhaled tobramycin
 - i. Inhaled aminoglycoside
 - ii. Recommended for initial *Pseudomonas* eradication therapy
 - (a) 28 days of therapy
 - (b) Monitor respiratory culture after completion to determine the presence of *P. aeruginosa*.
 - (c) The Early *Pseudomonas* Infection Control (EPIC) study showed that inhaled tobramycin plus ciprofloxacin was no more effective at *Pseudomonas* eradication than inhaled tobramycin alone.

- iii. Recommended for chronic use (28 days on and 28 days off cycled) in patients with CF having persistent *P. aeruginosa* from sputum culture
- iv. Use can be considered in younger patients.
- v. Dose: Tobramycin inhaled solution 300 mg nebulized twice daily, tobramycin dry powder for inhalation 112 mg = 4 capsules inhaled twice daily
- vi. Generally well tolerated, but some patients experience throat irritation, voice alterations, and hoarseness
- vii. Consider alternating with another inhaled antibiotic if patient has difficulty with symptoms in the off months.
- f. Inhaled aztreonam lysine
 - i. Inhaled monobactam antibiotic
 - ii. Recommended for chronic use (28-day cycles) in patients with CF having persistent *P. aeruginosa* from sputum culture
 - iii. Dosing: 75 mg nebulized three times daily using the specialized eFlow nebulizer; specific cleaning is required for this nebulizer
 - iv. Pretreatment with a bronchodilator is recommended.
 - v. Generally well tolerated, but some patients report bronchospasm and throat irritation
 - vi. Consider alternating with another inhaled antibiotic if patient has difficulty with symptoms in the off months.
- g. Inhaled colistin
 - i. Polymyxin antibiotic
 - ii. Intravenous formulation may be used off-label via inhalation for patients with resistant bacteria (i.e., *P. aeruginosa*)
 - iii. Can be used for chronic treatment every other month or for acute exacerbation treatment
 - iv. Dose: 75–150 mg of colistin base nebulized twice daily
 - v. Consider alternating with another inhaled antibiotic if patient has difficulty with symptoms in the off months.
- h. Ivacaftor (Kalydeco)
 - i. CFTR potentiator – Opens the CFTR channel to allow increased chloride transport
 - ii. Approved for patients 4 months and older
 - iii. Genotype: Patients need one responsive mutation (e.g., *G551D* and *R117H*); see package insert for details
 - iv. Dosage:
 - (a) Age 6 years and older: 150-mg tablet orally twice daily
 - (b) Age 6 months to 5 years and weight 14 kg or more: 75-mg granule packet orally every 12 hours
 - (c) Age 6 months to 5 years and weight 7 to less than 14 kg: 50-mg granule packet orally every 12 hours
 - (d) Age 6 months to 5 years and weight 5 kg to less than 7 kg: 25-mg granule packet orally every 12 hours
 - (e) Age 4 months to less than 6 months and weight 5 kg or more: 25-mg granule packet orally every 12 hours
 - (f) Dose adjustment in hepatic impairment
 - v. Administration: Take with fatty foods to increase absorption.
 - vi. Clinical trials showed increased FEV₁, weight, and quality of life and decreased sweat chloride.
 - vii. Adverse effects:
 - (a) Increased liver function tests – Monitor every 3 months of first year and then yearly.
 - (b) Headache
 - (c) Sore throat

- (d) Sinus congestion
 - (e) Runny nose
 - (f) Stomach pain
 - (g) Diarrhea
 - (h) Rash
 - (i) Nausea
 - (j) Dizziness
 - (k) Eye cataracts – In studies of young animals – Monitor at baseline and yearly in pediatric patients.
- viii. Drug interactions: CYP3A4 substrate – Dose adjustments may be needed for different medications.
- i. Ivacaftor/lumacaftor (Orkambi)
- i. CFTR modulator – Lumacaftor helps with stabilization for the CFTR protein, and ivacaftor increases channel opening to allow increased chloride transport.
 - ii. Approved for patients 2 years and older
 - iii. Genotype: F508del homozygous
 - iv. Take with fatty foods to increase absorption.
 - v. Dosing:
 - (a) Age 2–5 years
 - (1) Weight less than 14 kg: Lumacaftor 100 mg and ivacaftor 125-mg packet 1 orally every 12 hours
 - (2) Weight 14 kg or more: Lumacaftor 150 mg and ivacaftor 188-mg packet 1 orally every 12 hours
 - (b) Age 6–11 years: Lumacaftor 100 mg and ivacaftor 125 mg 2 tablets orally every 12 hours
 - (c) 12 years and older: Lumacaftor 200 mg and ivacaftor 125 mg 2 tablets orally every 12 hours
 - (d) Dose adjustment in hepatic impairment
 - vi. Clinical trials showed a small increase in FEV₁ and a decrease in pulmonary exacerbations.
 - vii. Adverse effects:
 - (a) Increased liver function tests – Monitor every 3 months for the first year and then yearly.
 - (b) Shortness of breath/chest tightness during initiation
 - (c) Eye cataracts – In studies of young animals – Monitor at baseline and yearly in pediatric patients.
 - (d) Dizziness
 - (e) Abnormal periods for women
 - (f) Sinus congestion
 - (g) Runny nose
 - (h) Diarrhea
 - (i) Nausea
 - (j) Rash
 - (k) Increased respiratory effects including chest discomfort and dyspnea, especially in patients with advanced lung disease
 - viii. Drug interactions
 - (a) Birth control – Hormonal birth control not recommended and is not a reliable form of birth control – Because of CYP3A4-mediated estrogen metabolism; alternative birth control option: intrauterine device
 - (b) CYP interactions – May need to change initial dosing if using with interacting medications
 - (c) Lumacaftor CYP3A4 strong inducer
 - (d) Ivacaftor CYP3A4 substrate

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- j. Ivacaftor/tezacaftor (Symdeko)
 - i. CFTR modulator – Tezacaftor helps with stabilization for the CFTR protein, and ivacaftor increases channel opening to allow increased chloride transport.
 - ii. Approved for patients 6 years and older
 - iii. Genotype: F508del homozygous or at least one responsive mutation, see package insert for details
 - iv. Dosage
 - (a) Age 12 years and older, or 6–11 years old, weight 30 kg or more: 1 tablet (tezacaftor 100 mg/ivacaftor 150 mg) in the morning and 1 tablet (containing ivacaftor 150 mg) in the evening – Take with fatty foods to increase absorption.
 - (b) Age 6–11 years, weight less than 30 kg: 1 tablet (tezacaftor 50 mg/ivacaftor 75 mg) in the morning and 1 tablet (containing ivacaftor 75 mg) in the evening – Take with fatty foods to increase absorption.
 - (c) Dose adjustment in hepatic impairment
 - v. Clinical trials showed increased FEV₁ and decreased pulmonary exacerbations.
 - vi. Adverse effects:
 - (a) Increased liver function tests – Monitor every 3 months for the first year and then yearly.
 - (b) Eye cataracts – In studies of young animals – Monitor at baseline and yearly in pediatric patients.
 - (c) Dizziness
 - (d) Sinus congestion
 - (e) Diarrhea
 - (f) Nausea
 - (g) Headache
 - (h) Rash
 - vii. Drug interactions
 - (a) CYP interactions – May need to change dosing if using with interacting medications
 - (b) Ivacaftor CYP3A substrate
 - k. Ivacaftor/tezacaftor/elexacaftor (Trikafta)
 - i. CFTR modulator – Tezacaftor and elexacaftor help with stabilization for the CFTR protein, and ivacaftor increases channel opening to allow increased chloride transport.
 - ii. Approved for patients 6 years and older
 - iii. Genotype: F508del homozygous and F508del heterozygous and if patients have one responsive mutation, see package insert for list
 - iv. Dosage
 - (a) Age 6–11 years and less than 30 kg: 2 tablets (elexacaftor 50 mg/tezacaftor 25 mg; ivacaftor 37.5 mg) in the morning and 1 tablet (containing ivacaftor 75 mg) in the evening – Take with fatty foods to increase absorption.
 - (b) Age 12 years and older: 2 tablets (elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning and 1 tablet (containing ivacaftor 150 mg) in the evening – Take with fatty foods to increase absorption.
 - (c) Dose adjustment in hepatic impairment
 - v. Clinical trials showed increased ppFEV₁ (percent predicted FEV₁) by 10%–13.8%, decreased pulmonary exacerbations by 63%, and increased body mass index.
 - vi. Adverse effects:
 - (a) Increased liver function tests – Monitor every 3 months for the first year and then yearly.
 - (b) Eye cataracts – In studies of young animals – Monitor at baseline and yearly in pediatric patients.
 - (c) Dizziness
 - (d) Diarrhea
-

- (e) Nausea
- (f) Headache
- (g) Rash
- vii. Drug interactions
 - (a) CYP interactions – May need to change dosing if used with interacting medications
 - (b) Ivacaftor CYP3A substrate
- l. Ibuprofen
 - i. Anti-inflammatory
 - ii. Recommended for patients 6–17 years of age, FEV₁ of 60% or greater to slow the loss of lung function
 - iii. No recommendation for or against in patients 18 years and older or in patients 2–5 years of age
 - iv. Dose: 20–30 mg/kg (max 1600 mg/dose) twice daily
 - v. Pharmacokinetic monitoring required; goal peak 50–100 mcg/mL
 - vi. Adverse effects: GI intolerance, nephrotoxicity, bleeding
 - vii. Increased risk of nephrotoxicity when used in combination with other nephrotoxic medications, including aminoglycosides. Concomitant use should be avoided.
- m. Inhaled β_2 -agonists
 - i. No recommendation for or against by CF guidelines
 - ii. Recommended pretreatment before hypertonic saline or inhaled aztreonam
- n. Therapies to avoid
 - i. Chronic oral corticosteroids or ICSs in the absence of asthma or allergic bronchopulmonary aspergillosis
 - ii. Prophylactic use of oral antistaphylococcal antibiotics
 - iii. Acetylcysteine nebulized – Oral is sometimes used for meconium ileus.
- 6. Acute pulmonary exacerbation treatment
 - a. Not well defined
 - b. Signs and symptoms include increased cough, increased sputum production, shortness of breath, chest pain, weight loss, and decreased lung function.
 - c. Treatment includes airway clearance and antibiotics.
 - i. Airway clearance: Increase frequency.
 - ii. Antibiotics: Recommended that antibiotics be selected according to present and past respiratory cultures and susceptibilities. The thick respiratory mucus of patients with CF makes it difficult to clear bacteria from the lungs.
 - (a) Common bacteria for empiric treatment: *P. aeruginosa*, MRSA, *Achromobacter xylosoxidans*, MSSA
 - (b) *P. aeruginosa*
 - (1) Recommended double-coverage – During exacerbations
 - (2) Typical regimen includes an antipseudomonal β -lactam and an aminoglycoside (typically tobramycin).
 - (3) Gentamicin is not recommended for routine use, given its nephrotoxicity risk.
 - (4) Once-daily aminoglycosides recommended (e.g., tobramycin 10 mg/kg/day intravenously every 24 hours; goal peak range 20–40 mcg/mL, trough goal less than 1 mcg/mL; AUC monitoring can also be used; example goal 75–125 mcg $\times$ hour/mL)
 - (c) MRSA
 - (1) Cause of significant lung function decline
 - (2) Consider treatment during exacerbations.
 - (3) Typical treatments
 - (A) Vancomycin
 - (B) Sulfamethoxazole/trimethoprim

(C) Linezolid

(D) Doxycycline or minocycline

- iii. Pharmacokinetic considerations for antibiotic dosing: Patients with CF renally clear antibiotics faster than do patients without CF and typically require higher, and sometimes more frequent, dosing.
 - (a) Increased volume of distribution
 - (b) Increased renal clearance
 - (c) Increased hepatic clearance
- iv. Treatment duration
 - (a) Duration is based on symptom and pulmonary function improvement.
 - (b) Studies suggest that the benefit of antibiotics decreases beyond 10–14 days of treatment.
 - (c) Antibiotics should be monitored (e.g., CBC, liver function tests, SCr), depending on the adverse effects associated with the medication.

E. Nutritional

- 1. High-calorie and high-fat diet recommended
- 2. Body mass index is correlated with lung function: Increased body mass index (greater than 50th percentile) = increased lung function
- 3. Pancreatic insufficiency
 - a. 85% of patients insufficient
 - b. Sludging of the pancreatic duct
 - c. Pancreas damaged early in the disease process
 - d. Treatment with pancreatic enzymes
 - i. Dosing: 500–2500 units of lipase/kg/meal (max 10,000 units of lipase/kg/day)
 - ii. Recommended starting dose: 1000 units of lipase/kg/meal
 - iii. Adjust dose according to stool fat content, steatorrhea, number of stools per day, and growth.
 - iv. Pancreatic enzymes include lipase, protease, and amylase.
 - e. Pancreatic enzymes currently available include capsules with encapsulated beads inside (one enzyme currently comes in tablet form). Capsules should be swallowed whole or opened and placed on applesauce.
 - f. Different brands of pancreatic enzymes have slightly different components and may not be interchangeable.
 - g. High doses of pancreatic enzymes have been associated with fibrosing colonopathy.
 - h. Immobilized lipase cartridge (Relizorb) can be used with overnight tube feeds. Pancreatic enzymes are released into the feedings.
- 4. Appetite stimulants
 - a. Can be used to increase appetite in patients
 - b. Cyproheptadine: 0.5 mg/kg/day: Sedation – A common adverse effect but decreases with continued use
 - c. Dronabinol: 2.5–5 mg twice daily: Euphoria and hallucinations can occur.
- 5. Multivitamins: CF-specific multivitamins contain higher amounts of fat-soluble vitamins A, D, E, and K.
 - a. Available as liquid, chewable tablets, and capsules
 - b. MVW Complete, Libertas, DEKA
- 6. Vitamins A, E, K
 - a. Yearly screen recommended with vitamin A and vitamin E concentrations
 - b. Vitamin K status can indirectly be assessed with PT/INR, or the PIVKA (protein induced by vitamin K absence) test can be used.
 - c. Supplementation of these vitamins is recommended when the patient's diet is deficient.

7. Vitamin D
 - a. Vitamin D is a fat-soluble vitamin.
 - b. Absorption is reduced in patients with CF.
 - c. Low vitamin D concentrations can lead to osteopenia or osteoporosis.
 - d. Recommended to check serum 25(OH)D concentrations to assess vitamin D status
 - e. Goal: 25(OH)D at least 30 ng/mL
 - f. Assess adherence to vitamin regimen in patients with low concentrations.
 - g. Supplementation is recommended with cholecalciferol (vitamin D₃) (Table 10).
 - h. Recommendations for vitamin D₃ supplementation are based on 25(OH)D concentration and age.
 - i. Do a repeat concentration 3 months after dose change.

Table 10. Vitamin D Supplementation in Cystic Fibrosis

	Birth – 1 Yr (IU/day)	1–10 Yr (IU/day)	10 Yr – Adult (IU/day)
Initial daily recommended dose	400–500	800–1000	800–2000
20–30 ng/mL	↑ to 800–1000	↑ to 1600–3000	↑ to 1600–6000
10–19 ng/mL	↑ to max of 2000	↑ to max of 4000	↑ to max of 10,000
< 10 ng/mL	Consult specialist/ assess for rickets	↑ to max of 4000	↑ to max of 10,000

IU = international units.

F. CF-Related Diabetes

1. Incidence: Children 2%, adolescents 19%, adults 40%–50%
2. Screening
 - a. Oral glucose tolerance test yearly starting at 10 years of age
 - i. Fasting glucose of 126 mg/dL or greater
 - ii. 2-hour glucose of 200 mg/dL or greater
 - b. A1C diagnostic if elevated, but does not rule out if low
3. Ketoacidosis and macrovascular effects are rare.
4. Treatment: Insulin
5. Typical regimens include mealtime coverage and basal plus bolus dosing.

G. Liver

1. Liver disease is not well understood.
2. Liver disease can range from biliary sludging to liver failure.
3. Ursodiol 20–30 mg/kg/day divided twice daily can be used for biliary sludging.

H. Allergic Bronchopulmonary Aspergillosis

1. Screen for yearly using IgE – High IgE (greater than 500 IU/L: consider further workup)
2. Allergic reaction to *Aspergillus* in sputum
3. Treatment: Oral corticosteroids for prolonged course; can consider antifungal treatment (itraconazole is the most studied)
4. Antifungal concentration monitoring is recommended, and achieving therapeutic concentrations can be difficult when antifungal agents are used with interacting medications (i.e., ivacaftor/lumacaftor).

I. NTM

1. Common environmental organisms
2. Prevalence increases with age.
3. Recommended to check an acid-fast bacilli (AFB) culture once a year in all patients with CF who can spontaneously expectorate sputum
4. If a patient has a past NTM-positive culture, an AFB culture should be obtained at every clinical interaction.
5. Do not use an oral pharyngeal swab for an AFB culture.
6. Susceptibility testing should be completed on positive AFB cultures and used to guide treatment.
7. Azithromycin – If positive for NTM, do not initiate chronic azithromycin three times a week, and if already receiving azithromycin, discontinue therapy; do not use azithromycin monotherapy when NTM is positive
8. Diagnosis of NTM pulmonary disease in patients with CF
 - a. Clinical diagnosis (both)
 - i. Pulmonary symptoms – Nodular or cavitary opacities
 - ii. Exclusion of other diagnosis
 - b. Microbiological diagnosis (one criterion)
 - i. Two expectorated sputum-positive cultures
 - ii. One BAL (bronchoalveolar lavage)-positive culture
 - iii. Biopsy with mycobacterial histopathologic features and positive culture or positive sputum culture
9. Treatment
 - a. *Mycobacterium avium* complex treatment (*M. avium*, *M. intracellulare*, *M. chimaera*)
 - i. Clarithromycin sensitive
 - (a) Macrolide daily (preferred azithromycin) plus rifampin plus ethambutol
 - (b) NEVER use monotherapy.
 - (c) Thrice-weekly regimen discouraged
 - (d) Consider an initial course of intravenous amikacin in severe disease.
 - ii. Clarithromycin resistant
 - (a) Amikacin intravenously plus rifabutin plus ethambutol plus quinolone (moxifloxacin) or clofazimine (clofazimine is not commercially available, and an FDA investigational new drug application is needed to obtain it)
 - (b) Collaboration with an expert in CF and NTM treatment is recommended.
 - iii. Duration
 - (a) 12 months beyond culture conversion
 - (b) Culture conversion: Three consecutive negative cultures
 - iv. Set up a drug monitoring plan at the beginning.
 - v. Repeat AFB cultures every 4–8 weeks during treatment.
 - b. *Mycobacterium abscessus* complex treatment (*M. abscessus*, *M. massiliense*, *M. bolletii*)
 - i. Intensive phase
 - (a) Daily oral macrolide plus intravenous amikacin plus one or more of the following: tigecycline, imipenem, ceftazidime
 - (b) Duration 3–12 weeks – Depending on severity, treatment response, and tolerability
 - (c) NEVER use monotherapy.
 - (d) Amikacin concentrations recommended for NTM are peaks of 20–30 mcg/mL and troughs less than 5–10 mcg/mL. Peaks recommended for NTM treatment are lower than those recommended for *Pseudomonas* treatment in patients with CF.

ii. Continuation phase

- (a) Oral daily macrolide plus inhaled amikacin plus two or three of the following: minocycline, clofazimine, moxifloxacin, linezolid
- (b) Guided by susceptibility but not dictated
- (c) Duration: 12 months beyond culture conversion (at least three negative cultures)
- (d) There is a potential for drug interactions with CFTR modulators and other CF medications that may require alterations or changes in regimens. Recommend to screen for drug interactions when starting and while on treatment

J. Distal Intestinal Obstruction Syndrome

1. Obstruction of the large intestine
2. Treatment: Bowel cleanout using polyethylene glycol 3350 or other laxatives
3. Surgical intervention is sometimes required.

Patient Case

Questions 6–9 pertain to the following case.

K.R. is a 6-year-old girl (weight 15.7 kg) with CF who was recently in the clinic for her regular appointment (F508del/R117H, FEV₁ 97% with some variability with effort). At the appointment, her parents reported no respiratory symptoms, a good appetite, and no concerns. Current medications include albuterol 2.5 mg nebulized twice daily, dornase alfa 2.5 mg nebulized daily, and 1 chewable vitamin A, D, E, K (contains 400 international units of vitamin D₃). At this clinic appointment, she had her yearly laboratory tests and a respiratory culture. Results are as follows:

Results:

Na 137 mmol/L	ALP 199 U/L	WBC 10.5 x 10 ³ cells/mm ³	PT 13.0 s
K 3.5 mmol/L	ALT 14 U/L	RBC 4.50 x 10 ³ cells/mm ³	INR 1.20
Cl 101 mmol/L	AST 20 U/L	Hgb 13.2 g/dL	IgE 16 IU/L
CO ₂ 27 mmol/L	Bili 0.5 mg/dL	Hct 37.3%	(25(OH)D) 21 ng/mL
BUN 10 mg/dL	GGT 12 U/L	MCV 83 fL	Vitamin A 33.1 mcg/dL
SCr 0.24 mg/dL	Total protein 6.7 g/dL	MCH 29.4 pg	
Glucose 90 mg/dL	Alb 3.1 g/dL	MCHC 35.4 g/dL	Vitamin E 1.2 mg/dL
Ca 9.3 mg/dL		RDW 12.7%	
		Plt 422,000/mm ³	

Bili = bilirubin; Ca = calcium; RDW = red cell distribution width.

Patient Case (continued)

K.R.'s current respiratory culture is *P. aeruginosa* and *H. influenzae* β -lactamase negative. Her past respiratory cultures are *Escherichia coli*, *H. influenzae*, and MSSA:

	MIC <i>Pseudomonas</i> Susceptibility
Piperacillin	≤ 4 S
Piperacillin + tazobactam	≤ 4 S
Ceftazidime	2 S
Cefepime	≤ 1 S
Imipenem	2 S
Gentamicin	4 S
Tobramycin	≤ 1 S
Ciprofloxacin	≤ 0.25 S
Colistin	S

MIC = mean inhibitory concentration.

6. Given K.R.'s respiratory cultures, which is the best recommendation for her therapy?
 - A. Inhaled tobramycin 300 mg inhaled twice daily for 28 days.
 - B. Inhaled tobramycin 300 mg inhaled twice daily for 28 days plus ciprofloxacin 300 mg orally twice daily for 28 days.
 - C. Inhaled tobramycin 300 mg inhaled twice daily for 28 days on and 28 days off cycles.
 - D. Inhaled vancomycin 250 mg inhaled twice daily for 28 days plus amoxicillin 470 mg orally three times daily for 28 days.
7. After K.R.'s antibiotic treatment, which would be the best follow-up?
 - A. CBC with differential and PT/INR.
 - B. Respiratory culture and BUN/SCr.
 - C. Respiratory culture.
 - D. BUN/SCr.
8. Because K.R.'s vitamin D concentration is low, which medication would best be added to her regimen?
 - A. Ergocalciferol 2000 international units orally daily.
 - B. Cholecalciferol 2000 international units orally daily.
 - C. Ergocalciferol 5000 international units orally daily.
 - D. Cholecalciferol 4000 international units orally daily.
9. K.R. is initiated on vitamin D supplementation. Which best answers the physician's question regarding when to repeat the vitamin D concentration?
 - A. 2 weeks.
 - B. 1 month.
 - C. 3 months.
 - D. 1 year.

IV. COMMUNITY-ACQUIRED PNEUMONIA

A. Background

1. In the United States, estimated to occur in 2.6% of children younger than 17 years
2. Worldwide incidence in children younger than 5 years includes 150–156 million cases and 2 million deaths per year.
3. Definition of pneumonia: Lower respiratory tract infection is typically associated with fever, respiratory symptoms, and evidence of lung parenchymal involvement (by examination or on chest radiography).

B. Community-Acquired Pneumonia (CAP)

1. Definition
 - a. Acute pulmonary infection
 - b. Previously healthy patient
 - c. Acquired in the community (not the hospital)
2. Cause by age group
 - a. Neonates (birth to 1 month)
 - i. Viruses
 - (a) Herpes simplex virus
 - (b) Enterovirus
 - (c) Adenovirus
 - ii. Bacteria
 - (a) Group B streptococci
 - (b) *Listeria monocytogenes*
 - (c) Gram-negative enteric bacteria
 - (d) *C. trachomatis*
 - (e) *S. pneumoniae*
 - (f) Anaerobes
 - b. Infants (1 month to 3 years)
 - i. Viruses – Most common cause
 - (a) Respiratory syncytial virus
 - (b) Influenza
 - (c) Parainfluenza
 - (d) Adenovirus
 - (e) Human metapneumovirus
 - ii. Bacteria
 - (a) *S. pneumoniae*
 - (b) *H. influenzae*
 - c. Children (3–5 years)
 - i. Viruses
 - (a) Respiratory syncytial virus
 - (b) Influenza
 - (c) Parainfluenza
 - (d) Adenovirus
 - (e) Human metapneumovirus
 - (f) Rhinovirus
 - (g) Coronaviruses

- ii. Bacteria
 - (a) *S. pneumoniae*
 - (b) *H. influenzae*
 - (c) *Moraxella catarrhalis*
 - (d) *S. aureus* (including community-acquired MRSA)
 - (e) *Streptococcus pyogenes*
- d. Children (older than 5 years)
 - i. Viruses: Respiratory
 - ii. Bacteria
 - (a) *S. pneumoniae*
 - (b) *Mycoplasma pneumoniae*
 - (c) *Chlamydia pneumoniae*, *Chlamydia psittaci*
 - (d) *Klebsiella pneumoniae*
 - (e) *S. pyogenes*
- 3. Signs and symptoms
 - a. Fever
 - b. Cough
 - c. Tachypnea
 - d. Increased work of breathing
 - e. Hypoxia
 - f. Infiltrate on chest radiography
- 4. Treatment
 - a. Outpatient
 - i. Preschool age
 - (a) Typically viral infections
 - (b) No antibiotics recommended
 - (c) If infection is suspected, see antibiotic recommendations in the text that follows.
 - ii. Infant to adolescent
 - (a) First line: Amoxicillin 90 mg/kg/day divided in two or three doses (max 4 g/day)
 - (b) Alternative: Amoxicillin/clavulanate 90 mg/kg/day divided in two doses (if using suspension, 600 mg/5 mL because of the amoxicillin/clavulanate ratio) – Can use if recent course of amoxicillin or β -lactamase–positive *H. influenzae* suspected
 - iii. Atypicals
 - (a) Coverage is recommended for school-aged children with symptoms of atypical pathogens.
 - (b) Add azithromycin 10 mg/kg on day 1 (max 500 mg), followed by 5 mg/kg/day on days 2–5 (max 250 mg/dose).
 - (c) Alternative: Clarithromycin
 - iv. Influenza
 - (a) Oseltamivir
 - (1) Premature infants: 2 mg/kg/day divided in two doses
 - (2) 0–11 months: 6 mg/kg/day divided in two doses (max 25 mg/dose)
 - (3) 12–23 months: 7 mg/kg/day divided in two doses
 - (A) 15 kg or less: 30 mg twice daily for 5 days
 - (B) 15–23 kg: 45 mg twice daily for 5 days
 - (C) Greater than 23 kg: See recommendations for children 2 years and older.
 - (4) 2–12 years and adolescents
 - (A) 15 kg or less: 30 mg twice daily for 5 days
 - (B) Greater than 15–23 kg: 45 mg twice daily for 5 days
 - (C) Greater than 23–40 kg: 60 mg twice daily for 5 days
 - (D) Greater than 40 kg: 75 mg twice daily for 5 days

- (b) If older than 5 years, can also use zanamivir
- b. Inpatient
 - i. Fully immunized
 - (a) First line: Ampicillin (150–200 mg/kg/day every 6 hours, max 12 g/day) or penicillin G (200,000–250,000 units/kg/day every 4–6 hours, max 24 million units/day)
 - (b) Alternative: Ceftriaxone (50–100 mg/kg/day every 12–24 hours, max 2000 mg/day)
 - (c) Add vancomycin (40–60 mg/kg/day every 6–8 hours, guidelines do not specify trough goals) or clindamycin (40 mg/kg/day every 6–8 hours, max 2700 mg/day) if community-acquired MRSA is suspected.
 - ii. Not fully immunized
 - (a) First line: Ceftriaxone (50–100 mg/kg/day every 12–24 hours, max 2000 mg/day)
 - (b) Alternative: Levofloxacin (16–20 mg/kg/day every 12 hours for age 6 months to 5 years and 8–10 mg/kg/day every 24 hours for those 5 years and older; max daily dose 750 mg)
 - (c) Add vancomycin (40–60 mg/kg/day every 6–8 hours, guidelines do not specify trough goals) or clindamycin (40 mg/kg/day every 6–8 hours, max 2700 mg/day) if community-acquired MRSA is suspected.
 - iii. Atypicals (*M. pneumoniae*)
 - (a) Coverage is recommended for school-aged children with symptoms of atypical pathogens.
 - (b) Add azithromycin 10 mg/kg on day 1 (max dose 500 mg), followed by 5 mg/kg/day on days 2–5 (max 250 mg/dose).
 - (c) Alternatives: Clarithromycin, erythromycin, doxycycline, levofloxacin
 - iv. Influenza
 - (a) Oseltamivir – See earlier dosing.
 - (b) If older than 5 years, can also use zanamivir
- c. If an organism is identified, antibiotic therapy can be tailored to that pathogen.
- d. Duration
 - i. 10 days is the most studied, though shorter courses may be effective.
 - ii. Community-acquired MRSA may require longer treatment.

Patient Case

Questions 10 and 11 pertain to the following case.

T.Y., a 1-year-old boy who presents to his pediatrician's office with fever and upper respiratory symptoms, is given a diagnosis of pneumonia.

- 10. Which antibiotic would be best to recommend for T.Y.'s pneumonia?
 - A. Amoxicillin/clavulanate.
 - B. Azithromycin.
 - C. Cefdinir.
 - D. Amoxicillin.
- 11. Which best represents the number of days that T.Y. should take the prescribed antibiotic?
 - A. 3.
 - B. 10.
 - C. 14.
 - D. 21.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

When assessing a patient's asthma control, it is important to assess for medication adherence, inhaler technique, environment factors, and comorbid conditions (Answer B is correct). Answer A is incorrect because the patient's height is not an essential factor in determining asthma control. Answer C is incorrect because, while family history can be a potential risk factor for getting asthma, it is not an important factor in assessing control. Answer D is incorrect because the patient has only one inhaler so the color of the inhaler will not be a factor.

2. Answer: B

Based on current symptoms, the patient's asthma is not well controlled and her home medications need to be stepped up. She is currently at step 1 of therapy. The preferred therapy in step 2 is a low-dose ICS and as-needed SABA. Answer A, budesonide DPI, is a medium-dose ICS, but a DPI would be difficult for a 6-year-old patient to use correctly. Answer C, the beclomethasone dose, is high and not low. Answer D, the budesonide dose, is high. Answer B is best because the fluticasone dose is a low-dose ICS, and the SABA as needed is included.

3. Answer: B

According to the GINA asthma guidelines, this patient's asthma is uncontrolled. He has been adherent to his medication, so his therapy should be increased by 1 or 2 steps. He is currently at step 2, a low-dose ICS; recommendations for step 3 therapy are daily and as-needed low-dose ICS-formoterol. Alternative therapies include a medium-dose ICS, a low-dose ICS/LABA, or low-dose ICS plus montelukast or theophylline. Recommendations for step 4 therapy are medium dose ICS-formoterol daily and as needed, medium-dose ICS/LABA, or medium dose ICS plus montelukast or theophylline. Answer A is incorrect because this is his current therapy. Answers C and D are incorrect because these ICSs plus LABAs are high-dose ICS options. Answer B is best because this is a medium-dose ICS.

4. Answer: C

Status asthmaticus is caused by inflammation in the airways, which must be reduced to resolve the exacerbation. Corticosteroids orally or intravenously at

1–2 mg/kg/day (max 60 mg/day) should be used with early administration (Answer C is correct). Because the patient's acute symptoms are covered with the albuterol/ipratropium treatments, the patient should receive the systemic corticosteroids next. Answer A is a supplemental treatment option if she does not respond to the albuterol/ipratropium treatments. Answer B is a treatment option, but because of its adverse effects and narrow therapeutic index, it should be reserved as a rescue medication. Answer D is the incorrect corticosteroid dose at only 0.33 mg/kg/day.

5. Answer: A

Terbutaline (Answer A) is a systemic β -adrenergic agonist that may help improve gas exchange. Answer B, ketamine, is not the best option, given its sedation adverse effects; ketamine can be used as salvage but would be used after terbutaline. Answer C, inhaled fluticasone, would not provide much benefit with this patient because he already takes systemic corticosteroids. Epinephrine (Answer D) can be used subcutaneously as a bronchodilator; however, it is not recommended for routine use in status asthmaticus.

6. Answer: A

This is the patient's first positive culture for *Pseudomonas*, so she requires eradication treatment. She is asymptomatic; therefore, she can be treated as an outpatient. Answer C is incorrect because she does not meet the criteria for a persistent *Pseudomonas* infection and does not need inhaled tobramycin cycles. Answer D is incorrect because these antibiotics do not treat *Pseudomonas*. Answer B is not the best option because the EPIC trial found no difference in eradication rates of inhaled tobramycin alone versus inhaled tobramycin plus ciprofloxacin orally. To reduce the medication burden, inhaled tobramycin alone for 28 days would be best (Answer A is correct).

7. Answer: C

A repeat respiratory culture is needed to determine whether the *Pseudomonas* eradication therapy was successful (Answer C is correct). Inhaled tobramycin solution has minimal systemic absorption, so checking the BUN and SCr would be unnecessary unless the patient had renal dysfunction at baseline (Answers B and D are

incorrect). A CBC with differential would be unnecessary because her previous CBC was normal (Answer A is incorrect).

8. Answer: B

The Cystic Fibrosis Foundation vitamin D guidelines recommend cholecalciferol for vitamin supplementation in patients with CF. For patients 12 months to 10 years of age with a vitamin D concentration of 20–30 ng/mL, the guidelines recommend increasing to the dose to 1600–3000 international units/day (Answer B is correct). Goal 25-25(OH)D concentrations in patients with CF are 30 ng/mL or greater. Answers A and C are incorrect because ergocalciferol is not the preferred vitamin D for supplementation in patients with CF. Answer D is incorrect because the dose is higher than needed for this vitamin D concentration.

9. Answer: C

The half-life of circulating 25(OH)D is about 2–3 weeks, so the approximate time of steady state is 12 weeks. The Cystic Fibrosis Foundation vitamin D guidelines recommend checking at a 3-month interval, which also coincides with the recommended every-3-month clinic visits (Answer C is correct). Answers A and B are incorrect because this is too soon to see the effect from vitamin D. One year (Answer D) is too long to wait to address the need for a change in vitamin D supplementation.

10. Answer: D

Amoxicillin is recommended for treating CAP in the outpatient setting, according to the Infectious Diseases Society of America guidelines (Answer D is correct). Amoxicillin/clavulanate (Answer A) is an alternative to amoxicillin. Azithromycin (Answer B) is not recommended as first-line treatment, and the patient is not school aged or at risk of atypical pneumonia. Cefdinir (Answer C) is an option for patients with penicillin allergies; however, it has poor bioavailability.

11. Answer: B

The CAP guidelines recommend a 10-day course (Answer B) of antibiotics for CAP. Total courses of 10 days are the most studied in this patient population. A shorter course might be sufficient, but 3 days (Answer A) of treatment would be insufficient. A longer course is not necessary for CAP (Answers C and D).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: B

The Infectious Diseases Society of America CAP guidelines recommend ampicillin (Answer B is correct) as first-line treatment for CAP in fully immunized hospitalized patients. Amoxicillin (Answer A is incorrect) is the recommended outpatient treatment, and the patient should be transitioned to amoxicillin once she has clinical improvement. Ceftriaxone (Answer C is incorrect) is recommended first line if the patient is not fully immunized. Clindamycin (Answer D is incorrect) is recommended in addition to ampicillin if the patient has risk factors for MRSA.

2. Answer: D

Eczema (Answer D is correct) is an atopic disease and a risk factor for developing asthma. Having a sibling with asthma (Answer A is incorrect) is not a major risk factor; however, having a parent with asthma would be a risk factor. This patient was only 36 weeks premature (Answer B is incorrect), which would not contribute to his risk, nor would his age (Answer C is incorrect).

3. Answer: C

This patient's culture has grown *P. aeruginosa*, which the Cystic Fibrosis Foundation recommends to double-cover while treating an exacerbation. This eliminates Answer B, because only one antibiotic is included, and Answer D, because ceftriaxone does not cover *P. aeruginosa*. Answer A is not the best option for this patient because piperacillin is a penicillin, and the patient has a penicillin allergy. In addition, the piperacillin dose is 120 mg/kg/dose every 8 hours, and the recommended piperacillin dose in patients with CF at standard infusion times is at least 100 mg/kg/dose every 6 hours. Answer C is correct because cefepime and tobramycin will double-cover *P. aeruginosa*, and both are dosed correctly.

4. Answer: A

The patient has CAP (Answer A is correct) because her symptoms began less than 48 hours into her hospitalization. If the symptoms had occurred more than 48 hours into her hospitalization or if she had had previous contact with the hospital, her pneumonia would have been hospital acquired (Answer B is incorrect). Her pneumonia is not ventilator associated because she is

receiving noninvasive respiratory support (Answer C is incorrect), and her symptoms are not consistent with a necrotizing pneumonia (Answer D is incorrect).

5. Answer: C

The patient's difficult social situation will make medication adherence challenging. Dexamethasone (Answer C is correct) 1- to 2-day courses were shown in a meta-analysis to be as effective as a 5-day course of prednisolone (Answer A is incorrect) in preventing return visits for patients with asthma leaving the ED. The dexamethasone 2-day option is best for this patient, given its ease of adherence and long half-life. The maximum dexamethasone dose per day is 16–18 mg. Hydrocortisone (Answer D is incorrect) is not recommended for asthma exacerbations. Given the patient's history, he would unlikely adhere to a 7-day course of methylprednisolone (Answer B is incorrect).

6. Answer: A

This patient is newly initiated on pancreatic enzymes, and the recommended starting dose according to the CF nutrition guidelines is 1000 units of lipase per kilogram per meal. The dose of 2 capsules of the 6000 units of lipase capsules (Answer A is correct) will give this patient 1090 units of lipase per kilogram per meal. This dose can be adjusted according to the patient's response to therapy. The doses of 3, 4, and 5 capsules per meal (Answers B–D are incorrect) are above the recommended starting dose.

7. Answer: B

Based on her symptoms, the patient's asthma is not controlled and she needs to step up on her asthma treatment (Answer A is incorrect). The patient is currently on step 1 of therapy, and step 2 is a low-dose ICS and as-needed SABA. Answer B is correct because this is a low-dose ICS for this age group. Answers C and D are incorrect because these are more than low-dose ICS.

8. Answer: D

This patient was previously healthy and has no risk factors for community-acquired MRSA (Answer A is incorrect). *S. pneumoniae* (Answer D is correct) is the most common pathogen for CAP in children. The patient is fully immunized, so *H. influenzae* (Answer

C is incorrect) is unlikely. *C. trachomatis* (Answer B is incorrect) can cause pneumonia in infants of mothers infected with *C. trachomatis*, but it is unlikely to occur in this age group.

9. Answer: C

Although the patient reports no symptoms, her FEV₁ is decreased from baseline, which is of concern and should be treated (Answer A is incorrect). She is older than 6 years, so hypertonic saline (Answer C is correct) is recommended as maintenance therapy, which may help increase the FEV₁ back to baseline. Increasing pancrelipase (Answer B is incorrect) is unnecessary because the patient has no GI symptoms and is stooling well. Answer D is incorrect because ICSs are not recommended by the Cystic Fibrosis Foundation for patients with CF.

10. Answer: A

This patient's vitamin D concentration is below the goal of 30 ng/mL recommended by the CF vitamin D guidelines. With a concentration of 23 ng/mL, the guidelines recommend assessing patient adherence to current vitamins and, if the patient is adherent, increasing vitamin D by 1600–6000 units/day (Answer A is correct). This patient's vitamin A and E concentrations were normal (Answers B and C are incorrect), as was his INR (Answer D is incorrect); hence, the other vitamins need not be added to his treatment regimen.

11. Answer: A

This patient's asthma is classified according to the GINA guidelines as partly controlled because of nighttime awakening, exacerbations giving 1 point. The recommendation is to increase by 1 step. She is currently on step 3 of therapy with a low-dose ICS and LABA combination. Step 4 is the preferred option is a medium-dose ICS plus a LABA. Answer A is a medium-dose ICS plus a LABA option (Answer A is correct). Answer B is not the best option because this is just a high-dose ICS with no additional agent. Answer C is a low-dose ICS plus a LABA. Answer D is a high-dose ICS; however, the LABA component in the combination product is above the recommended dose.

12. Answer: C

This patient currently takes a medium-dose ICS plus montelukast, and her asthma is classified as well

controlled. Because her asthma has been controlled for at least 3 months, her therapy can be stepped down by 1 step. Next is step 3, which gives the option of a low-dose ICS. The preferred therapy is daily and as-needed low-dose ICS plus formoterol and other alternatives include: medium-dose ICS and as-needed plus plus a LABA or a low-dose ICS plus montelukast. Answer A is an increase in therapy, making it incorrect. Answer B is incorrect because it is the current therapy. Answer C is correct because this is a low-dose ICS, and Answer D is incorrect because this is a high-dose ICS plus a LABA.

13. Answer: B

Because this patient has ongoing symptom control while receiving inhaled tobramycin and is having no adverse effects, inhaled tobramycin should be continued as part of her regimen (Answers A and C are incorrect). Because she has difficulty with symptoms in the tobramycin off months, she may benefit from *Pseudomonas* coverage with inhaled aztreonam during this time (Answer B is correct). Answer D is not the best option because her culture is not growing MRSA, and from her symptom report, that does not appear to be the issue.

PEDIATRIC PUBLIC HEALTH AND PATIENT ADVOCACY

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PEDIATRIC PUBLIC HEALTH AND PATIENT ADVOCACY

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Learning Objectives

1. Describe the limitations regarding the regulation of medication use and availability in the pediatric population, and describe how the pediatric clinical pharmacy specialist can affect, inform, and address these limitations through advocacy and awareness.
 2. Define organizations and resources available to support and advocate for specialized training and competency for the role of a pediatric clinical pharmacy specialist.
 3. List health care initiatives aimed at promoting safe and effective medication use in the pediatric population.
 4. Describe the role of pediatric clinical pharmacy specialist in advocating for the inherent challenges of caring for the pediatric population.
2. Which most accurately names the law that requires studies for drug use and labeling in pediatric patients only for the same indications as approved in adults?
 - A. Kefauver-Harris Drug Amendment.
 - B. Orphan Drug Act.
 - C. Best Pharmaceuticals for Children Act (BPCA).
 - D. Pediatric Research Equity Act (PREA).

Abbreviations in This Chapter

ASHP	American Society of Health-System Pharmacists
BPCA	Best Pharmaceuticals for Children Act
CAM	Complementary and alternative medicine
CHIP	Children's Health Insurance Program
ETS	Environmental tobacco smoke
OTC	Over the counter
PAH	Pulmonary arterial hypertension
PREA	Pediatric Research Equity Act

Self-Assessment Questions

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

1. Which best summarizes why medication use in pediatric patients can be challenging?
 - A. There are pharmacodynamic and pharmacokinetic differences within the pediatric population.
 - B. Dosing is commonly weight based and not standardized compared with dosing in the adult population.
 - C. Ability to predict adverse effects may not be as clear as in the adult population.
 - D. The lack of evidence-based information in the pediatric population is an inherent disadvantage.
2. Which best describes the challenges with orphan drugs?
 - A. Both PREA and BPCA require that orphan indications be studied in drug development.
 - B. Novel treatments with no pediatric- or adult-only data for asthma would fall under orphan drugs.
 - C. Because rare disease states seldom occur, the cost to study orphan drugs to treat such disease states can be prohibitive.
 - D. The Orphan Drug Act requires a decelerated drug development to ensure enough patients are studied.
3. Which best describes the benefit of both PREA and BPCA in pediatric patients?
 - A. BPCA encompasses all of PREA plus biologics.
 - B. Conducting pediatric drug studies is voluntary.
 - C. Indications for pediatric use can be expanded.
 - D. Goal is to establish appropriate use and labeling.
4. Which best describes the challenges with orphan drugs?
 - A. Both PREA and BPCA require that orphan indications be studied in drug development.
 - B. Novel treatments with no pediatric- or adult-only data for asthma would fall under orphan drugs.
 - C. Because rare disease states seldom occur, the cost to study orphan drugs to treat such disease states can be prohibitive.
 - D. The Orphan Drug Act requires a decelerated drug development to ensure enough patients are studied.
5. You are asked about the novel use of a drug to treat a rare metabolic disorder in a neonatal patient. You know from the U.S. Food and Drug Administration (FDA) indication that its use would be off-label. Which reference is best known for containing off-label uses?
 - A. *AHFS Drug Information* (book).
 - B. Manufacturer's package insert.
 - C. Lexicomp *Pediatric & Neonatal Dosage Handbook*.
 - D. Micromedex NeoFax: For neonatal drug information.
6. There is a shortage of alprostadil. You are helping the pharmacy operations manager devise a conservation plan for the patients who need this agent for maintaining patent ductus arteriosus. You are

- approached by an attending neonatologist, who asks whether the pharmacy can begin stocking alprostadil vials on the unit because there is concern about accessing the drug. Which is the best answer?
- A. Inform him that alprostadil is on shortage; however, stocking alprostadil vials in the unit is the best action possible.
 - B. Explain that alprostadil vials will not be stocked on the unit so that the pharmacy can help ensure that use of alprostadil vials is limited to maintaining a patent ductus arteriosus.
 - C. Explain that although you understand the need, stocking alprostadil vials in the unit would lead to waste of the remainder of the vial.
 - D. Agree to his request because alprostadil is a life-sustaining product that should be readily accessible at all times.
7. Which best describes the purpose of the National Institute for Children's Health Quality?
- A. To improve child health by improving the systems of children's health care.
 - B. To improve child health by requiring research studies of pediatric patients.
 - C. To improve child health by encouraging drug manufacturers to conduct pediatric research.
 - D. To improve child health by ensuring access for children to innovative, safe, and effective medical products.
8. A first-year pediatric medical resident asks you for assistance with treating otitis media in an 18-month-old girl. The resident would like to use intramuscular ceftriaxone to treat the ear infection, and the patient is receiving calcium gluconate in her total parenteral nutrition. The resident recalls an interaction between these two drugs but not the details. Which is the best response regarding this combination?
- A. Calcium gluconate should be removed from the total parenteral nutrition, and calcium supplementation should be changed to an oral formulation, if possible.
 - B. Azithromycin is a better treatment than ceftriaxone for otitis media because of a potential interaction with the patient's oral calcium supplements.
 - C. There are no data on interactions between intramuscular ceftriaxone and intravenous calcium products.
 - D. Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated because of the patient's age.
9. In the clinic where you work, the parent of a child you often care for mentions he has begun using e-cigarettes as a way to quit smoking. Which statement is most accurate?
- A. Transitioning to e-cigarettes is a good smoking cessation strategy and will not place the child's health at risk.
 - B. E-cigarettes have become the most commonly used tobacco product in children, teens, and young adults.
 - C. Aside from nicotine, e-cigarettes are free of toxic chemicals.
 - D. Children are less vulnerable to the effects of environmental tobacco smoke (ETS) because they usually have healthier respiratory systems than adults.
10. A third-year pediatric resident on his cardiology rotation consults with you regarding a 9-year-old boy with pulmonary arterial hypertension (PAH). The resident is concerned because the patient is being treated with oral sildenafil citrate, and the resident was previously taught to avoid this agent for this particular indication. Which is the best response to this resident's concern?
- A. Sildenafil use is contraindicated in pediatric patients with PAH, and an alternative agent should be used instead.
 - B. The FDA recommends against using sildenafil in pediatric patients.
 - C. Sildenafil is not FDA approved for children younger than 12 years, so it should not be used in this patient.
 - D. Studies have shown that medium-dose sildenafil produces favorable results, but further information is needed to compare the relative risk-benefit of sildenafil use in pediatric patients.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

Domain 4: Public Health and Patient Advocacy; Task(s) 4.1, 4.2, 4.3, 4.4

I. ADVOCACY FOR THE PEDIATRIC PATIENT POPULATION IN HEALTH CARE POLICY

- A. Pediatric clinical pharmacy specialists can directly and indirectly affect the health of the pediatric population. This includes advocating within the institution where they work as well as on the local, state, and national levels by their awareness of and engagement in public health policy efforts through professional organizations.
1. Examples of pharmacy-related public health issues in the pediatric population:
 - a. The epidemic of childhood obesity
 - b. Over-the-counter (OTC) medication misadventures
 - c. Vaccinations
 - d. Drug shortages
 - e. Medical marijuana
 - f. Pharmacogenetic considerations in breastfeeding (e.g., codeine)
 - g. Antimicrobial misuse
 - h. Opioid epidemic
 - i. Availability of specialty pharmacy services
 - j. Lack of pediatric formulations of medications
 - k. Mental/behavioral health crisis
 2. Pediatric clinical pharmacy specialists can affect public health issues through awareness, engagement, and advocacy by incorporating pediatric population health efforts into clinical practice:
 - a. Advocating for considerations due to pediatric obesity
 - b. Educating on the risks associated with OTC medications
 - c. Raising awareness regarding the importance of childhood vaccinations by:
 - i. Providing vaccination screening
 - ii. Informing the public about state and local immunization programs
 - iii. Being aware of vaccine hesitancy and providing evidence-based facts to dissipate misconceptions
 - d. Understanding the impact of drug shortages on the pediatric population
 - e. On a state level, advocating for regulations on medical marijuana packaging and standardization of product: Childproof packaging of medical marijuana products
 - f. Pharmacogenetic considerations for medication use in pediatrics. Examples:
 - i. Informing providers about the risks associated with using codeine for postoperative pain control in children who are undergoing a tonsillectomy and/or adenoidectomy (T and A) procedure. Fatalities have occurred in ultra-rapid metabolizers of codeine, due to toxic morphine concentrations
 - ii. Educating new mothers about the risk of breastfeeding when taking codeine-containing products and recognizing signs of toxicity in the infant
 - g. Implementing pediatric-specific antimicrobial stewardship programs
 - h. Advocating for safe opioid prescribing, naloxone availability, and widespread education to children and adolescents regarding the risks of opioid misuse
 - i. A prospective study published in 2017 found that 58% of opioid doses dispensed on discharge to children with acute pain were not consumed.
 - ii. Only 19% of families were educated on proper disposal of the remaining opioids, and of those, only 4% of families disposed of the medication.
 - iii. Unconsumed opioids may contribute to the opioid epidemic through diversion.
 - i. Advocating for the utilization of pediatric specialty pharmacies
 - i. Specialty pharmacies can cater to the pediatric patient population needs such as access to medications that require special handling, tailored dosage forms, and high cost medications for rare or complex disease states.

- B. The pediatric patient population as a group has an inherent disadvantage with respect to evidence-based information about drug safety and efficacy. “Off-label” dosing and indications are common in pediatric pharmacotherapy. Many reasons and complexities must be considered because of the differences in the pediatric patient population compared with the adult population.
1. FDA oversight:
 - a. Role is to protect and promote public health.
 - b. The pediatric population is a minority with respect to research and FDA drug approval.
 - c. 20% of the drugs approved by the FDA are estimated to have been approved for pediatric use.
 2. Importance of public awareness:
 - a. Caregivers often do not realize that their child is being treated with a drug that is not approved for use in pediatric patients or that use is off-label from the approved indications.
 - b. The pediatric clinical pharmacy specialist’s role is to inform the caregiver/patient of how safety and efficacy will be ensured when drugs are used off-label. A reference that should be readily available to the pediatric clinical pharmacy specialist is the *AHFS Drug Information* (book), which contains medically accepted uses of drugs, both on-label and off-label.
 3. Risks of adverse drug events with off-label drug use in pediatric patients are often unknown until harm has occurred. Examples include:
 - a. Tetracycline-induced dental dysplasia: Intrinsic discoloration caused by structural change and mineralization into the tooth enamel, leading to a brown-tinged discoloration
 - b. “Gray baby syndrome” with chloramphenicol: In 1960, Weiss et al. described gray baby syndrome in the *New England Journal of Medicine*. This occurred because of the neonate’s immature hepatic function. The infants could not metabolize the drug because of immature glucuronidation (specifically glucuronyl transferase) as well as their inability to excrete the unconjugated drug. This led to severe adverse events, described as abdominal distension, skin discoloration caused by progressive cyanosis, vasomotor collapse, and death.

Patient Case

1. A second-year medical resident on rotation in the neonatal intensive care unit calls you because the attending neonatologist has asked to use chloramphenicol in a 14-day-old, 28-week neonate who had a positive blood culture for a gram-negative organism that is susceptible to only two drugs, including chloramphenicol. Which best explains why chloramphenicol should not be used?
 - A. Only 20% of FDA-approved drugs are estimated to be approved for pediatric use, and chloramphenicol is no different.
 - B. Chloramphenicol use in neonates is off-label; it should thus be avoided unless no other treatment options exist.
 - C. Adverse events can occur regarding chloramphenicol use in the neonatal population, and you would advise him to weigh the risk-benefit.
 - D. Chloramphenicol should only be used in neonates if there is no other treatment option because of the risk of death caused by immature liver function.

C. Reasons for the Lack of Research in Pediatric Patients:

1. Parents/guardians may have perceived risks of participating in drug research.
2. The inherent differences in pharmacodynamics and pharmacokinetics compared with those in adults
3. Dosing is weight based and not standard compared with that of adults.
4. Ability to predict adverse effects or adverse events may be unclear.

5. The challenge of obtaining informed consent and assent in patients 7 years and older
 6. Emancipated minors have the legal rights of an adult with the clinical considerations of a pediatric patient.
 7. Parent/guardian may not understand the purpose of the research.
- D. As a result, laws have been established to improve medication safety and evaluate medication efficacy in the pediatric population.
1. Kefauver-Harris Drug Amendment of 1962 to the Food, Drug, and Cosmetic Act: Required the demonstration of safety and efficacy of drugs and biologics for human use before FDA approval and marketing, excluding the pediatric population
 2. The following two laws work hand-in-hand to promote drug and biologic research in the pediatric population.
 - a. In 2002, Congress passed BPCA to advocate the research of new and existing drugs in the pediatric patient population. This has allowed manufacturers to qualify for an additional 6 months of patent exclusivity if they complete pediatric studies, thereby providing a financial benefit.
 - b. In 2003, PREA was enacted, which allows the FDA to require pediatric studies. PREA requires pharmaceutical companies to evaluate medication safety and efficacy in pediatric patients if the indication is the same as the FDA-approved indication in adults (see Table 1).

Table 1. Evaluation of PREA and BPCA

FDA Pediatric Drug Development Law	PREA	BPCA
Coverage	Covers drugs and biologics	
Studies	Mandatory	Voluntary
Indication studies	Only on FDA-approved indications under review	Can expand indications
Orphan indication studies	Orphan indications are exempt	Orphan indication studies can be requested
Labeling	Pediatric labeling can only be used for FDA-approved adult indications	
Goal	Appropriate use and labeling of drugs and biologics used in pediatric patients	

BPCA = Best Pharmaceuticals for Children Act; PREA = Pediatric Research Equity Act.

Information from: Office of New Drugs Unit List: Pediatric Regulations. Available at www.accessdata.fda.gov/scripts/cder/world/index.cfm?action=newdrugs:main&unit=4&lesson=1&topic=8#:~:text=PREA%20is%20the%20stick%20of%20the%20legislator.%20Ultimately%2C.

- E. Orphan Drugs and Rare Disease States in Pediatric Patients
1. A rare disease state is defined as affecting fewer than 200,000 U.S. patients.
 2. Around 95% of rare diseases lack an FDA label–approved drug for treatment.
 3. Obtaining FDA approval for drugs to treat rare diseases can be challenging because the treatment is often expensive and will benefit only a few patients because of the low incidence of the disease.
 4. These drugs are often the only treatment option to improve quality of life and, in severe cases, can be life sustaining.
 5. Orphan Drug Act: Passed in 1983 and provides incentive for developing orphan drugs
 - a. Created the FDA Office of Orphan Products Development
 - b. Created a strategic plan for accelerating the development of therapies for rare pediatric diseases
 - c. Supported the development and marketing of more than 400 drugs and biologic products for rare diseases

6. Examples of drugs for rare disease states or indications in the pediatric population that have, or had, FDA orphan status:
 - a. Rilpivirine: Treatment of neuroblastoma
 - b. Eltanexor: Treatment of myelodysplastic syndrome
 - c. Ketamine hydrochloride: Treatment of status epilepticus
 - d. Insulin-like growth factor-1: Treatment of Duchenne muscular dystrophy
 - e. Enzastaurin: Treatment of Ehlers-Danlos syndrome
 - f. Bictegravir/emtricitabine/tenofovir alafenamide: Treatment of HIV type 1 infection in pediatric patients
 - g. Casimersen: Treatment of Duchenne muscular dystrophy
 - h. Glecaprevir and pibrentasvir: Treatment of pediatric patients with chronic hepatitis C virus infection
 - i. Ionapegsomatropin-tcgd: Treatment of growth hormone deficiency
 - j. Voxelotor: Treatment of sickle cell disease
- F. FDA Office of Pediatric Therapeutics:
 1. Primary goal is to ensure access for children to innovative, safe, and effective medical products because:
 - a. Medical products have not been tested for use in children
 - b. Pediatric product development studies require additional protection for children
 2. The FDA Office of Pediatric Therapeutics has four components:
 - a. Scientific activities program: Ensures that pediatric studies are rigorously designed and conducted
 - b. Ethics program: Supports FDA efforts to ensure that children are only enrolled in clinical studies that are both scientifically necessary and ethically appropriate
 - c. Safety program: Coordinates the mandated pediatric-focused safety review by the Pediatric Advisory Committee for drug and biologic products 18 months after labeling changes in response to voluntary and required pediatric studies
 - d. International program: Facilitates communication and collaboration between the FDA and partner regulatory agencies around the world

II. IMPORTANCE OF AGE-APPROPRIATE DOSAGE FORMS, PRODUCT LABELING, AND PEDIATRIC POPULATION-SPECIFIC CONSIDERATIONS

- A. Pediatric patients are not small adults, and age-appropriate dosing goes beyond weight-based dosing.
- B. Improved safety for the pediatric patient by advocating for improved product labeling and limitation of multiple concentrations of the same medication. Examples include, but are not limited to, the following:
 1. Discontinuation of OTC infant concentration of acetaminophen from the market to avoid confusion over varying acetaminophen concentrations
 2. FDA public health advisory against using OTC cough and cold products in those younger than 2 years
 - a. Overdose and misuse of these products have been implicated in infant deaths.
 - b. Literacy and numeracy rate among caregivers directly affects the potential for misinterpreting the labeling.
 3. Efforts by American Society of Health-System Pharmacists (ASHP) and Institute for Safe Medication Practices (ISMP) to standardize intravenous and oral concentrations of medications to reduce errors by standardization in all healthcare settings.
 - a. ASHP created and endorsed standardized intravenous and oral concentrations medication lists (www.ashp.org/Pharmacy-Practice/Standardize-4-Safety-Initiative?loginreturnUrl=SSOCheckOnly).

- b. ISMP has published recommendations for standardized concentrations for neonatal drug infusions to minimize medication errors in this vulnerable patient population. Support for the use of standardized concentrations for neonatal drug infusions to minimize medications errors in this vulnerable patient population have been well established.
- C. The Epidemic of Childhood Obesity
 1. Raising awareness about the increasing incidence of childhood obesity
 2. Training of health care professionals on childhood obesity interventions and dosing considerations
 3. Providing recommendations to providers regarding dosing adjustments to prevent underdosing or overdosing
- D. Examples of Pediatric-Specific Dosing Tools and References:
 1. Use of enteral or oral dosing syringes for improved accuracy in delivering oral doses compared with the household teaspoon, and use of oral dosing syringes instead of intravenous syringes for liquid medications in the hospital
 2. Syringes that measure volumes less than 1 mL for both oral and intravenous doses
 3. Commonly used pediatric-specific drug references:
 - a. Lexicomp *Pediatric & Neonatal Dosage Handbook*
 - b. Micromedex NeoFax: For neonatal drug information
 - c. American Society of Health-System Pharmacists: *Pediatric Injectable Drugs* (The Teddy Bear Book)
 4. Syringe pumps for accurate administration of low-dose/rate intravenous infusions and an extra dose range check for mg/kg dosing
- E. Risks and Mitigations for Addressing the Lack of Age-Appropriate Dosage Forms
 1. Risks caused by the lack of age-appropriate dosage forms
 - a. Dosage forms that require manipulation before administration can lead to error. Risk of harm is greater with high-alert medications such as opiates, insulin, and heparin.
 - b. Dose calculation errors are the most common medication error in neonatal and pediatric practice. For example, milligrams per kilogram per day can easily be confused with milligrams per kilogram per dose, which can lead to:
 - i. Supratherapeutic doses
 - ii. Subtherapeutic doses
 - c. Lack of standard concentrations for extemporaneous oral liquids between inpatient and outpatient pharmacies can lead to errors (under-/over-dosing)
 2. Age-Appropriate, Commercially Available, and Extemporaneously Compounded Products
 - a. Commercially available oral solutions should readily be stocked in the pharmacy caring for the pediatric population.
 - b. Pharmacies that extemporaneously compound products for the pediatric patient should have the following readily available:
 - i. References for extemporaneous compounds to meet the needs of the pediatric patient population. Examples of references for extemporaneous compound recipes:
 - (a) Lexicomp *Pediatric & Neonatal Dosage Handbook*
 - (b) American Society of Health-System Pharmacists publications such as *Extemporaneous Formulations for Pediatric, Geriatric, and Special Needs Patients*
 - ii. A standardized departmental database with formulations and specific instructions for compounding with citations
 - iii. Guidance using USP 795 nonsterile compounding requirements to ensure safety and quality
 - iv. Policies and procedures for the training and competency assessment of pharmacy personnel compounding these products and quality checks to ensure accuracy

F. Age-Appropriate Considerations for Drug Administration

1. Ability to swallow tablets or capsules
2. Proper use of inhalation devices with or without a spacer
3. Appropriate volume considerations in the neonatal population
4. Intravenous tubing considerations for small volumes to ensure adequate drug delivery
5. Injectable medications requiring dilution – Example: Dilution of fentanyl 50 mcg/mL injection to make a measurable concentration for small doses
6. Medication product packaging intended for the adult population – Increased costs to dispense:
 - a. Personnel time to prepare the products in patient-specific doses (age-/weight-based)
 - b. Increased material costs related to:
 - i. Dilutions needed to make a ready-to-administer concentrations for the pediatric patient
 - ii. Waste because of smaller doses needed or medications with short expirations. Examples:
 - (a) Epoprostenol infusion preparations; a small portion of the manufacturer's vial is used, and the remainder of the vial expires before the next dose is needed
 - (b) Intravenous acetaminophen packaged as a 1-g single-use vial; to dispense a weight-based dose, less than 1000 mg, the remainder of the vial must be wasted

G. Publication of the KIDs List in 2020: Key Potentially Inappropriate Drugs in Pediatrics

1. Similar to the Beers Criteria for the older adult population, the KIDs List is a reference tool aimed at identifying medications associated with a high risk of adverse drug reactions within the population.
2. The KIDs List is intended to serve as a guideline for clinical practice and to help improve medication safety. Additionally, it raises awareness of potentially inappropriate medications for pediatrics.
3. Examples of medications on the KIDs List include:
 - a. Benzocaine (risk: methemoglobinemia)
 - b. Sulfonamides (risk: kernicterus)
 - c. Meperidine (risk: respiratory depression)

III. MEDICATION ERROR PREVENTION IN THE PEDIATRIC PATIENT THROUGH AUTOMATION AND TECHNOLOGY**A. Use of health care informatics can improve overall health care outcomes in a health system.****B. Automation and technology are generally developed for the adult population and often need manipulation and retrofitting to meet the needs of pediatric patients.**

1. Computerized physician order entry (CPOE) can minimize prescribing errors, with some caveats.
 - a. Decision support: Functionality within the CPOE system that can help guide the user in reducing medication errors and increase the effective use of medications and laboratory tests (e.g., dose rules and best practice alerts)
 - b. Dose rules: A set of predetermined dosing guidelines that are entered into the CPOE system that cross-reference the medication order and alert the provider of any deviation from these values
 - i. CPOE systems come with vendor-supplied dose rules for medications. These dose rules may not address the dynamic differences within the pediatric population and also may have gaps in the dosing rules, for example, for the neonatal population; subspecialty patient considerations within pediatrics such as the pediatric patient with cystic fibrosis
 - ii. Traditional pediatric clinical references are often more accurate and all-encompassing than vendor-supplied dosing rules.
 - iii. Manipulation of the vendor-supplied dose rule is essential to meet the needs of the pediatric patient population, but this can lead to human error. Free-text dose rule entry can be used, but it can be time- and resource-intensive and can create manual entry errors.

- c. Pediatric clinical pharmacy specialists can play an integral role by providing feedback to their informatics department or advocate through professional organizations to provide CPOE vendors with insight on making the system pediatric friendly.
- 2. Programmable infusion pumps (e.g., smart pumps)
 - a. Standard concentrations and pediatric-specific dosing limits may decrease the risk of medication errors for intravenous medications when using infusion pumps in the pediatric patient population.
 - b. Advocacy through professional organizations specific to pediatric patients is needed to encourage manufacturers to create pumps that program in units per kilogram per hour rather than standard units per hour, which is typically used in the adult population. Potential for medication errors exists when back-extrapolating to adult dosing units. Example: Pump requires milliliters per hour, but drug is dosed in milliliters per kilogram per hour. The programmer would need to back-extrapolate so that the units match the programming points.
 - c. The FDA has recognized the need to improve the safety of programmable infusion pumps. In August 2016, the FDA Safety Communication issued guidelines regarding fluid flow continuity at low infusion rates with the goals of:
 - i. Increasing awareness about limitations of syringe pumps to infuse therapies at low rates which is common in the pediatric population
 - ii. Increasing awareness of the lack of flow continuity, resulting in serious clinical consequences, delay of therapy, overinfusion, or underinfusion
 - d. Institute for Safe Medication Practices (ISMP) also published “Guidelines for Optimizing Safe Implementation and Use of Smart Infusion Pumps” in 2020, which can be used to advocate for the safe use in pediatric patients.
- 3. Bar-coded medication administration (BCMA)
 - a. BCMA can reduce harm in the pediatric and neonatal populations, particularly with high-risk medications such as opiates, heparin, and insulin.
 - b. The need for individualized doses can be a challenge because each dose needs to have a reliable barcode. Some products lack a barcode, which leads to the creation of custom barcodes. This introduces the risk of a barcode being attached to the wrong product or manual barcoding when unit dosing bulk medication for use in the pediatric population can lead to a breakdown in the integrity of the BCMA system, if not done accurately.
- 4. Limitations with using automated dispensing devices and cabinets
 - a. In the pediatric population, the need for dispensing patient-specific dosages is increased because of weight-based and age-appropriate dosing. As a result, facilities with a pediatric population have an increased need for patient-specific pharmacy dispensing compared with the adult population, which uses more standardized dosing.
 - b. Pediatric clinical pharmacy specialists can advocate for safe medication delivery by educating health care professionals on the considerations needed when using floor stock medications in automated dispensing devices. This includes measures such as drawing up partial doses from intravenous vials or unit-dosed liquid cups, and splitting tablets.

IV. MANAGING DRUG SHORTAGES, ADVOCATING FOR DRUG ALLOCATION TO THE PEDIATRIC PATIENT, AND CONSIDERATIONS UNIQUE TO THE PEDIATRIC PATIENT POPULATION

A. National Federal Advocacy on Drug Shortages

- 1. FDA: Center for Drug Evaluation and Research drug shortage program. In 2013, the FDA published a strategic plan for preventing and mitigating drug shortages, and subsequently published “Drug Shortages: Root Causes and Potential Solutions” in 2019.
- 2. The Centers for Medicare & Medicaid Services has also published guidelines on how to manage drug shortages of formulary medications.

- B. Drug allocation and restriction are often necessary to ensure that the supply on hand is distributed to the appropriate patient population. Why this is effective in the pediatric population:
1. Critical need for the drug on shortage because of high-volume usage in pediatrics (e.g., parenteral nutrition in neonates)
 2. Lack of acceptable alternative dosage forms which can lead to errors:
 - a. Oral solutions and suspensions. If an oral solution or suspension is on backorder, there may be no alternative recipe to extemporaneously compound the solution or suspension.
 - b. Alternatively, the concentration may differ from the commercial product.
 3. Intravenous products:
 - a. A preservative-free option may be unavailable, which can be a risk in the neonatal period because of preservatives, such as benzyl alcohol accumulation, and potential toxicity.
 - b. The concentration of alternative intravenous products may require manipulation to safely deliver the correct dose to the patient (e.g., morphine 10 mg/mL diluted to a concentration that allows for accurate measurement for small doses).
 4. Oral tablets and capsules: Alternative strengths may be inappropriate for weight-based dosing, leading to the need for manipulation in aliquots and estimation of the dose.
 5. Inhaled products: Depending on their age, pediatric patients may be unable to effectively use inhaled dosage forms such as metered-dose inhalers or dry powder inhalers to correctly deliver the dose.
- C. Joint position statements during the public health crisis making pharmacists stewards of health care resources. For example: Due to the COVID-19 pandemic, the American Medical Association, American Pharmacists Association, and ASHP issued a joint statement providing guidance, which could impact the pediatric patient population directly and indirectly regarding the following:
1. Personal protective equipment
 2. Safety and adverse events
 3. Evidence-based medication use
- D. Lack of Clinically Viable Therapeutic Alternatives
1. Can occur because of the lack of data or lack of FDA-approved indications for pediatric use to guide treatment alternatives
 2. Use of therapeutic alternatives may also lead to increased adverse effects because of pediatric-specific differences in ADME (absorption, distribution, metabolism, and excretion), such as immature liver function and decreased protein binding.
 3. In the adult population, there may be several well-established treatment alternatives from different therapeutic classes to treat a condition. In the pediatric patient population, there may be only one established drug used to effectively treat a certain condition. Examples of pediatric conditions that have only one viable treatment option:
 - a. Endogenous prostaglandins (alprostadil [prostaglandin E1]): Used to maintain ductus patency in the neonate, therefore providing added circulation until cardiac surgery
 - b. Arginine: Used to treat neonatal inborn errors of urea synthesis that can lead to life-threatening hyperammonemia
 4. Oncology medications often lack therapeutically equivalent alternatives (e.g., methotrexate shortage, which is important in the treatment of pediatric leukemia), which may lead to suboptimal treatment and potentially poor outcomes.
 5. During drug shortages, vials or larger package sizes may be necessary to provide the drug for patients.
 - a. Can lead to waste of a package when only a small amount is used for a pediatric dose
 - b. Can also lead to the need to aliquot or unit-dose into smaller doses without adequate stability and sterility data

V. PEDIATRIC ADVOCACY THROUGH PROFESSIONAL ORGANIZATIONS, FEDERAL AGENCIES, AND ACCREDITING BODIES**A. Professional Organizations**

1. Participation in local, state, and national associations can increase awareness of pediatric patients' unique needs.
2. National pharmacy associations that serve as resources for pediatric patient care:
 - a. American Society of Health-System Pharmacists
 - i. Pediatric networking session at the Midyear Clinical Meeting: Pediatric-specific programming resource for managing drug shortages
 - ii. Section of clinical specialists and scientists of the pediatric advisory group charged with developing educational programs and resources for members in pediatric pharmacy practice
 - iii. Accreditation for postgraduate year one (PGY1) residencies in freestanding children's hospitals
 - iv. Accreditation for postgraduate year two (PGY2) residencies in pediatric pharmacy
 - b. American College of Clinical Pharmacy
 - i. Pediatrics PRN: A forum for professional interaction and networking that leads to opportunities for collaborative research, problem solving, and professional discussion of issues relevant to pediatric pharmacotherapy
 - ii. Pediatric-specific programming
3. Pediatric-specific organizations
 - a. Pediatric Pharmacy Association: Association promoting safe and effective medication use in children
 - i. Annual meeting with various subspecialty focuses within pediatrics
 - ii. Subcommittees focusing solely on advocacy, among other key topics in pediatrics
 - iii. Pediatric-specific research
 - iv. Platform and poster presentations
 - b. Children's Oncology Group: Multi-institutional group focusing on cancer therapy optimization through standard protocols while balancing morbidity and mortality
 - c. Children's Hospital Association: Consortium of freestanding children's hospitals. Advocates for purchasing power and contract pricing across the group, which otherwise would be a minority in the scheme of several adult health care systems. Also participates in pediatric-related research and data comparison across the consortium
 - d. Cystic Fibrosis Foundation:
 - i. Multi-institutional research
 - ii. Specialty pharmacy services
 - iii. Therapeutic guidelines for managing cystic fibrosis

B. Regulatory and Consulting Agencies That Affect Pediatric Health Care

1. National Institute for Children's Health Quality is an independent nonprofit organization that seeks to improve child health through improving the systems of children's health care.
2. ISMP is a nonprofit organization for safe medication use and the prevention of medication errors. ISMP is a resource for relevant and pertinent medication safety information.
 - a. ISMP medication safety alert newsletters
 - b. Medication safety tools: High-alert medication lists and look-alike, sound-alike medication lists
 - c. Quarterly watch reports: Monitor for serious adverse drug events
 - d. Medication Error Reporting Program (ISMP MERP)
 - e. Safety position statements, guidelines, risk assessments, toolkits, and other resources
3. FDA
 - a. Resource for pediatric research
 - b. MedWatch reporting for adverse events

- c. Vaccine Adverse Event Reporting System – comanaged with the Centers for Disease Control and Prevention
- 4. The Joint Commission
 - a. Sets pediatric-specific medication management standards
 - b. Informs about sentinel event alerts
 - c. Establishes standards for safe medication practices

VI. IMPORTANCE AND VALUE OF POSTDOCTORAL PEDIATRIC-TRAINED PHARMACY SPECIALISTS AND PEDIATRIC CLINICAL SPECIALISTS

- A. Additional postdoctoral training is essential because there is a lack of pediatric-specific training nationwide in pharmacy school curriculums.
 - 1. Recent joint statement by Cox et al. (Am J Pharm Educ 2020;84:ajpe7892) advocates for the need for pediatric-specific education.
 - a. Pediatric patients make up about 25% of the population.
 - b. Pharmacist knowledge base across the lifespan is an Accreditation Council for Pharmacy Education requirement.
 - c. Outlines recommendations on how to incorporate pediatric specialty training into pharmacy education.
- B. Advocacy for Postdoctoral Training – Can be as straightforward as requiring formal training in pediatric pharmacotherapy for any pharmacist working in a pediatric clinical setting. The American College of Clinical Pharmacy PRN opinion paper “Recommendations for Meeting the Pediatric Patient’s Need for a Clinical Pharmacist” outlines the vision for the minimum training requirements for pharmacy specialists caring for pediatric patients:
 - 1. Provides the framework that administrators can use for job justification for pediatric pharmacy residency programs
 - 2. Endorses PGY2 programs as essential for providing optimal patient outcomes in specialty areas such as pediatrics
 - 3. In addition, various organizations have described and endorsed the importance of pediatric pharmacy training, including:
 - a. American College of Clinical Pharmacy
 - b. American Academy of Pediatrics
 - c. American Society of Health-System Pharmacists
 - d. Pediatric Pharmacy Association
 - 4. Financial justification for pediatric pharmacy residency programs has its limitations due to the lack of Medicaid pass-through funding. Return on investment for pharmacy residency positions can be shown by the following:
 - a. Documentation of resident contributions (e.g., monographs, medication interventions, research) annually
 - b. Quantifying operational staffing
 - c. Utilization of pharmacy residents as clinical extenders
- C. Impact on Clinical Outcomes in Pediatric Patients and Demonstration of Return on Investment of the Pediatric Clinical Specialist to the Health Care System, Patient, and Payers:
 - 1. The return on investment includes both cost and quality impact.
 - 2. With specialized training in pediatrics, pharmacy specialists can impact the following:
 - a. Decreased length of stay

- b. Decreased overall health care costs
 - c. Decreased adverse drug reactions
 - d. Improved outcomes from an efficacy and safety standpoint
 - e. Serve as an essential member of the patient care team. For example, the Centers for Medicare & Medicaid Services requires a pharmacy specialist as part of the transplant team.
 - 3. Based on the opinion paper by LaRochelle et al. (J Am Coll Clin Pharm 2020;3:786-92), pharmacist participation in pediatric patient care has been shown to have a positive impact on clinical outcomes in the following:
 - a. Medication error avoidance
 - b. Antimicrobial stewardship
 - c. Drug monitoring
 - d. Opioid dependence
 - e. Medication access
 - f. Pulmonology
 - g. Hematology
 - h. Immunology
 - 4. Due to specialized training in pediatric pharmacotherapy, pediatric clinical specialists are uniquely set up to make interventions specific for the needs of the pediatric patient.
 - 5. Based on the described impact on clinical outcomes and potential for cost savings, pediatric clinical specialists are an essential member of the pediatric healthcare team.
- D. Competency and Standardized Training
- 1. Pediatric-specific competencies – Foremost are core competencies in general pediatrics:
 - a. Pharmacokinetics
 - b. Pharmacodynamics
 - c. Common pediatric disease states
 - d. Medication safety
 - e. Pediatric nutrition
 - f. Pediatric dosing resources and literature interpretation
 - 2. In pediatric medicine, subspecialties exist that are similar to those in the adult population as well as some that are unique to pediatric patients such as genetic and metabolic disorders.
 - a. Examples of subspecialized competency areas for pediatric clinical pharmacy specialists:
 - i. Pediatric intensive care unit
 - ii. Neonatal intensive care unit
 - iii. Pediatric nutrition
 - iv. Pediatric emergency care
 - v. Pediatric cardiology
 - vi. Pediatric infectious disease
 - vii. Pediatric oncology, hematology, and bone marrow transplantation
 - b. Demonstration of competency in pediatrics should be required before independently caring for a pediatric patient. These qualifications can include, but are not limited to, the following:
 - i. Postgraduate training
 - ii. Completion of an institution-based competency program
 - iii. Pediatric advanced life support certification (PALS)
 - iv. Board certification as a pediatric pharmacy specialist (BCPPS)
 - 3. Key opinion papers supporting the pediatric pharmacy specialty training and the pediatric pharmacist role can be found under references at the end of this chapter.

VII. DRUG WARNINGS AND INFORMATION INVOLVING THE PEDIATRIC POPULATION

- A. Pharmacists should report adverse events associated with prescription and OTC medications using the online FDA Safety Information and Adverse Event Reporting Program called MedWatch (<https://www.accessdata.fda.gov/scripts/medwatch/>).
1. Reporting is voluntary and can be used to report suspected or observed adverse events to the following products:
 - a. Prescription or OTC medications
 - b. Biologics (including blood components, blood and plasma derivatives, allergenics, human cells, tissues, and cellular and tissue-based products)
 - c. Medical devices
 - d. Special nutritional products (dietary supplements, infant formulas, and medical foods)
 - e. Cosmetics
 - f. Foods/beverages
 2. Examples of FDA initiatives that have resulted from reporting, in addition to clinical research, are outlined in the text that follows.
 - a. Cough and cold products in children younger than 6 years
 - i. In 2007, an FDA Advisory Panel in a split vote recommended against using antihistamines, decongestants, antitussives, and expectorants in children younger than 6 years. This recommendation was a result of increasing evidence of misuse that has resulted in overdose and even death, especially in children younger than 2 years.
 - ii. This recommendation was limited to the treatment of symptoms of the common cold (i.e., excluded treatment of allergies).
 - iii. The panel cited the lack of scientific testing related to safety and efficacy in children as the rationale for the recommendation. A summary of the studies are in the text that follows:
 - (a) No studies support the safety and efficacy of cough and cold medications in children younger than 2 years.
 - (b) A 1993 review assessing OTC cough and cold medications in preschool children showed that these medications were not associated with symptom relief.
 - (c) In 2002, a systematic review found OTC cough medications no more effective than placebo in relieving symptoms of acute cough associated with an upper respiratory infection.
 - (d) A study surveying the parents of children who were given dextromethorphan, diphenhydramine, or placebo for nocturnal cough and sleep difficulty associated with an upper respiratory infection found that neither medication was superior to placebo in nocturnal symptom relief.
 - (e) A 2004 Cochrane review concluded that evidence was insufficient to determine the effectiveness of OTC medications for acute cough in adults or children.
 - iv. This recommendation resulted in several manufacturers of OTC children's cough and cold products voluntarily withdrawing their products from the market.
 - v. Clinicians should recommend the following measures for cough and cold symptoms:
 - (a) Make sure the child gets plenty of rest and fluids.
 - (b) Use a rubber suction bulb to clear an infant's clogged nose. Saline nose drops can be used to soften secretions.
 - (c) Use a cool mist humidifier in the child's room. Clean and dry the humidifier regularly.
 - (d) Acetaminophen or ibuprofen can be used to alleviate pain or fever. Caregivers should confirm that these medications contain no additional ingredients.

- b. Ceftriaxone use with calcium-containing products in neonates
 - i. In 2007, the FDA released information to health care professionals related to the interaction of ceftriaxone with calcium-containing products, according to reports of fatal cases in neonates. Fatalities were associated with both simultaneous administration of ceftriaxone and calcium-containing products and administration at separate times and through different infusion lines.
 - ii. FDA recommendations and considerations included the following:
 - (a) Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates. Ceftriaxone should not be used in neonates if they are receiving (or are expected to receive) calcium-containing intravenous products.
 - (b) In patients older than 28 days, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.
 - (c) Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions by a Y-site in any age group.
 - (d) Do not reconstitute or mix ceftriaxone with a calcium-containing product.
 - (e) There are no data on interactions between intravenous ceftriaxone-containing and oral calcium-containing products or between intramuscular ceftriaxone and intravenous or oral calcium-containing products.
- c. Codeine and tramadol toxicity in children – In 2012, the FDA issued a drug safety communication regarding the risk of rare, but life-threatening adverse events or death related to codeine use in children after a tonsillectomy and adenoidectomy (T&A) procedure. Ultra-rapid metabolizers of cytochrome P450 (CYP) 2D6 convert codeine to morphine more rapidly and to a greater extent than do people without this polymorphism.
 - i. Communication was prompted by:
 - (a) Reports of children 2–5 years of age who developed severe adverse effects (three deaths and one life-threatening respiratory depression) after receiving codeine for T and A postoperative pain management. Three of the patients were ultra-rapid CYP2D6 metabolizers.
 - (b) A case report describing the death of a breastfeeding infant whose mother was receiving codeine for postpartum pain. The mother was an ultra-rapid metabolizer of CYP2D6, and her breast milk contained high concentrations of morphine. Tramadol and its active metabolite are also found in breast milk and are associated with the same risks as codeine in ultra-rapid metabolizers.
 - ii. A black box warning was added to the prescribing information for all codeine-containing products concerning the risk of use for postoperative pain management in children after a T and A procedure.
 - iii. The FDA issued new information regarding this safety report in 2017, which included the following drug label changes:
 - (a) Contraindication restricting the use of codeine and tramadol to treat pain in children younger than 12 years
 - (b) Contraindication regarding tramadol use in children younger than 18 years after a T and A procedure
 - (c) Warning recommending against using codeine and tramadol in children 12–18 years of age who have obesity or conditions that increase the risk of serious breathing problems, such as obstructive sleep apnea or severe lung disease. The safety update was based on a review of several adverse event reports submitted to the FDA, including:
 - (1) 64 cases of serious breathing problems and 24 deaths with codeine-containing medications in children younger than 18 years

- (2) Nine cases of serious breathing problems and three deaths with tramadol use in children younger than 18 years
- iv. In 2018, an additional FDA safety announcement required label changes to prescription cough and cold medications containing codeine and hydrocodone to restrict their use in children younger than 18 years.
- v. The FDA determined that the risks of slowed or difficult breathing, misuse, abuse, addiction, overdose, and death outweighed the benefits of these medications in the pediatric population.
- d. Lidocaine and benzocaine used to treat teething
 - i. In 2018, the FDA announced all over-the-counter teething products with benzocaine need to be removed from market.
 - ii. Topical pain relievers are ineffective because they wash out of the infant's mouth within minutes.
 - iii. Lidocaine overdose when used for teething has resulted in seizures, brain injury, and cardiac issues. A black box warning and additional information were added to the warning and dosing sections of the prescribing information for prescription viscous lidocaine 2%, warning against this practice.
 - iv. Benzocaine use has been associated with methemoglobinemia, a rare but serious condition that results in a large decrease in oxygen carried through the blood.
 - v. Parents and caregivers should follow American Academy of Pediatrics recommendations for treating teething pain:
 - (a) Use a teething ring chilled in the refrigerator (not the freezer).
 - (b) Gently rub or massage the child's gums with fingers to relieve symptoms.
- e. Sildenafil use in children with PAH: In 2012, the FDA issued a drug safety communication recommending against sildenafil use in children with PAH. Interim results of the STARTS-2 study (Sildenafil in Treatment-Naive Children, Aged 1–17 years, with Pulmonary Arterial Hypertension) showed a higher mortality ratio for patients receiving high-dose therapy (20–80 mg, depending on weight).
 - i. The hazard ratio for the high-dose group compared with the low-dose group (10 mg) was 3.5 ($p=0.015$).
 - ii. Deaths reported were related to worsening PAH, and most patients who died had baseline hemodynamic values above the study median.
 - iii. The authors concluded that medium-dose sildenafil produced favorable results, whereas low-dose therapy showed no benefit. Further studies are needed to determine optimal dosing strategies.
 - iv. In 2014, the FDA clarified the statement that their recommendation was not intended to say it should never be used.
 - v. Further information is needed to compare the relative risk-benefit of sildenafil use in pediatric patients because guidance is currently unclear for managing PAH in infants and children.
 - vi. Sildenafil use in pediatric PAH remains controversial because patients are currently being treated successfully with this agent without adverse effects. Common sense is needed because not treating PAH will cause death.
- f. Seizures associated with cefepime use in renal impairment – In 2012, the FDA issued a drug safety communication related to the risk of nonconvulsive status epilepticus (NCSE) in patients with kidney impairment receiving cefepime without adequate dosage adjustment.
 - i. Reports of NCSE linked to cefepime use were identified in the FDA's Adverse Event Reporting System (AERS) database, and although cases were primarily in older adult patients, incidents occurred in children as young as 7 years.
 - ii. In addition to the AERS database, case reports of this adverse event have been reported in two other pediatric patients (a 15-year-old male adolescent and a 15-year-old female adolescent).

- g. Corrected QT interval (QTc) prolongation with ondansetron
 - i. In 2012, the FDA issued a drug safety communication related to the potential for ondansetron to prolong the QTc interval and increase the risk of developing torsades de pointes.
 - ii. Ondansetron already had this adverse effect listed in its prescribing information, but new information prompted the FDA to strengthen the warning. This communication followed reports of additional cases of QTc prolongation in pediatric patients. One case report described a previously healthy 11-year-old girl who developed polymorphic ventricular tachycardia within minutes of receiving ondansetron and dimenhydrinate.
- h. Diazoxide use in infants and newborns
 - i. The FDA (2015) has warned that pulmonary hypertension has been reported in infants and newborns treated with diazoxide.
 - ii. Eleven cases of pulmonary hypertension have been identified in infants and newborns treated with diazoxide since the drug was approved in 1973.
 - iii. In all cases, the pulmonary hypertension resolved or improved when the drug was discontinued.
 - iv. The FDA recommends closely monitoring patients receiving diazoxide, especially patients at high risk of pulmonary hypertension. Diazoxide should be discontinued if the patient develops pulmonary hypertension.
- i. General anesthetic and sedation drugs in young children: In 2017, the FDA approved label changes regarding the use of general anesthetic and sedation medication in children younger than 3 years.
 - i. A new warning was added to drug labels stating that cumulative exposure to these medications (long periods of administration or several surgical procedures) may negatively affect brain development in children younger than 3 years.
 - ii. The FDA warns that surgical procedures should not be delayed or avoided if medically necessary; however, the potential to delay elective surgical procedures should be considered, if appropriate.

Patient Case

2. R.S. is a 14-year-old male adolescent, previously healthy, who presents to the emergency department with a broken arm. The resident would like to prescribe tramadol and asks if you agree. The patient weighs 85 kg (body mass index [BMI] 31.6 kg/m², greater than 95th percentile). Which is the most appropriate response?
- A. Recommend against using tramadol because tramadol is contraindicated in all children younger than 18 years.
 - B. Recommend using tramadol in this patient because he is older than 12 years and did not recently undergo a T and A procedure.
 - C. Recommend against using tramadol because the patient has obesity.
 - D. Recommend against using tramadol and suggest the provider use a hydrocodone-containing product because it has more safety and efficacy data in pediatric patients.

VIII. COMPLEMENTARY AND ALTERNATIVE MEDICINE

- A. The National Center for Complementary and Integrative Health (formerly the National Center for Complementary and Alternative Medicine) estimates that 12% of American children have used or been given a complementary health product or practice.
 - 1. Up to 10% of infants are given teas or botanical supplements for fussiness or stomach problems.
 - 2. Teens are more likely to use products that claim to enhance sports performance, energy levels, and weight loss.

3. More than 50% of children with a chronic medical condition are likely to use a form of complementary and alternative medicine (CAM), usually together with conventional care.
- B. The most commonly used CAM approaches in children are herbal and botanical products (not including vitamins and minerals) and chiropractic or osteopathic manipulation.
- C. The most common conditions for using CAM approaches in children include the following.
 1. Back or neck pain
 2. Head or chest colds
 3. Anxiety or stress
 4. Other musculoskeletal problems
 5. Attention-deficit/hyperactivity disorder
 6. Insomnia
 7. Refractory seizures
- D. As in the adult patient population, many CAM approaches have not been tested for safety and effectiveness in the pediatric population. Caregivers should be counseled that:
 1. Children may react differently than adults to CAM approaches.
 2. Federal regulations for dietary supplements are less strict than those for prescription and OTC drugs.
 3. Some dietary supplements may be of poor quality or contain contaminants, including drugs, chemicals, or metals.
 4. CAM approaches should not replace or delay conventional care or prescribed medications.
 5. Discuss any CAM approaches that patients may use with the health care providers involved in their care.

IX. CHILDHOOD POISONING

- A. Poison Prevention – Pharmacists should advocate and inform caregivers to:
 1. Keep medications and other products stored in their original containers.
 2. Read the entire label before taking or giving medication.
 3. Use medication only as directed by your physician, your pharmacy specialist, or the label.
 4. Call medication by its proper name, not “candy.”
 5. Take medication where children cannot watch because children learn by imitating adults.
 6. Use child-resistant packaging. Replace the caps tightly.
 - a. The Poison Prevention Packaging Act (PPPA) of 1970 requires several household substances to be packaged in child-resistant packaging. The U.S. Consumer Product Safety Commission promulgated regulations pursuant to this legislation, which can be found at 16 CFR Parts 1700–1702.
 - b. Packaging must be designed or constructed to be significantly difficult for children younger than 5 years to open within a reasonable time, and not difficult for normal adults to use properly.
 - c. For older adults and those with disabilities who might have difficulty opening such containers, the PPPA requires that a regulated product available for purchase on store shelves be packaged in one noncomplying size, provided it carries a warning that it is not recommended for use in households with children. Regulated prescription drugs may be dispensed in non–child-resistant packaging if specifically requested by the prescribing physician or the patient.
 - d. Since in effect, remarkable declines have been reported in children’s deaths from ingestions of toxic household products, including medications.
 7. Lock medications and household products where children cannot see or reach them.
 8. Store household products in a place different from food and medication.
 9. Keep purses and briefcases out of children’s reach.

10. Use carbon monoxide detectors.
11. Have the Poison Control number readily available (1-800-222-1222).

Patient Case

3. A mother who calls the outpatient pharmacy at your pediatric facility is frantic because her 19-month-old daughter just swallowed a great deal of Elmer's glue. She has syrup of ipecac on hand and wants your advice on what to do next. Which is the best response to this mother's request?
 - A. Call Poison Control at 1-800-222-1222.
 - B. Take the patient immediately to the nearest emergency department.
 - C. Administer syrup of ipecac and call 911.
 - D. Contact the child's pediatrician for next steps.

X. VACCINES

- A. Immunizations are considered by many experts the most effective preventive health measure, saving many from death or serious disability.
- B. Despite the evidence to support the efficacy and safety of vaccines, it remains a controversial issue for many parents because the diseases they prevent have become much less common, and caregivers are less familiar with the effects of vaccine-preventable diseases.
- C. All 50 states in the United States require some immunizations before school entry; however, parents can exempt their children from immunizations.
- D. Three Types of Exemptions:
 1. Medical
 2. Religious
 3. Philosophical
- E. All states allow medical exemptions for children who have a valid medical contraindication to a vaccine or component of the vaccine, almost all allow exemptions on the basis of religious beliefs, and 30% allow philosophical exemptions for individuals with a moral or philosophical belief against some or all immunizations.
- F. The Pediatric Infectious Diseases Society is opposed to legislation that allows philosophical exemption to mandatory vaccines because studies suggest that states allowing philosophical exemptions have significantly higher exemption rates than do states with medical exemptions only. These states also have higher rates of vaccine-preventable diseases. Caregivers tend to selectively vaccinate against diseases they believe are more severe and refuse vaccines for diseases they believe are not dangerous. The varicella vaccine is one of the most commonly refused vaccines.
 1. Vaccine refusal consequently increases the risk of vaccine-preventable disease in unvaccinated individuals and increases the risk of vaccine-preventable disease outbreaks in the general population. For example, in 2017, a measles outbreak in Minnesota led to 65 confirmed measles cases. Ninety-five percent occurred in unvaccinated individuals.

2. In 2015, the United States had a multistate measles outbreak linked to Disneyland in California. Of the 125 measles cases reported, 110 involved California residents. Among the 110 residents, 45% were unvaccinated and 43% had an unknown or undocumented vaccination history.
 3. On March 11, 2020, the World Health Organization declared COVID-19 a global pandemic.
 - a. By the end of March 2020, the U.S. Department of Health & Human Services created an “Operation Warp Speed” program tasked with expediting a COVID-19 vaccine.
 - b. In December 2020, the FDA issued emergency use authorizations for both Pfizer and Moderna COVID-19 vaccines for individuals 18 years of age and older and later expanded to 12 years of age and older for the Pfizer vaccine in May 2021.
 - c. FDA approval of the Pfizer COVID-19 vaccine was official in August 2021 for individuals 12 years of age and older.
 - i. Children 5–11 years of age were granted an emergency use authorization for the Pfizer vaccine in October 2021.
 - ii. A survey of parents with children less than 18 years of age in a major metropolitan area reported a COVID-19 vaccine hesitancy rate of 33% for their child.
 - (a) This parental hesitancy rate is higher than data from other studies for routine vaccines (6.1%) and annual influenza vaccine (25.8%).
 - (b) Including children in vaccination efforts and plans is imperative for increasing community protection against COVID-19.
- G. Common Concerns Include:
1. Autism caused by the measles, mumps, and rubella (MMR) vaccine, despite overwhelming evidence showing that MMR and autism occur independently
 2. Concerns that the HPV (human papillomavirus) vaccine promotes early sexual activity, which have been proven unfounded
 3. Vaccine association with Guillain-Barré syndrome
 4. Mercury-related neurologic effects associated with thimerosal exposure, including the development of autism. Several studies refute this hypothesis.
 5. Concerns that vaccines are associated with sudden infant death syndrome; however, several research studies have found no causative relationship
- H. Pharmacists can be influential health care providers, educating vaccine-hesitant caregivers using the following recommendations:
1. Use positive dialogue with caregivers that presumes they will ultimately vaccinate their child.
 2. Establish open, ongoing, nonconfrontational dialogue to identify any concerns.
 3. Target education to the caregiver’s specific concerns.
 4. Use schedules that deviate from recommended schedules only if other options have failed and caregivers would otherwise refuse vaccines entirely.

Patient Case

4. J.C. is a 6-year-old girl who is brought to the clinic for the treatment of acute otitis media. On reviewing her medications, you notice she has not received any vaccinations. You ask the child's mother why. The child's mother endorses concern that the preservative thimerosal may have negative effects on her daughter's neurologic function. Which is the best way to respond to this parent?
- A. Inform the parent that her concern is invalid because the thimerosal dose in vaccine products is too low to cause harm.
 - B. Acknowledge the parent's concern, but inform her that vaccines no longer contain thimerosal.
 - C. Acknowledge the parent's concern and inform her that several studies have shown that vaccines do not cause mercury-related neurologic effects associated with thimerosal exposure.
 - D. Acknowledge the parent's concern and provide general information regarding the importance of vaccinations.

I. Online Resources That Pharmacists Can Refer Concerned Parents to Include:

- 1. www.vaccinesafety.edu
- 2. www.vaccine.org
- 3. www.vaccinateyourfamily.org
- 4. www.immunize.org
- 5. www.immunizationinfo.org
- 6. www.vaccineinformation.org
- 7. www.cdc.gov/vaccinesafety/concerns/

XI. SECONDHAND SMOKE AND TOBACCO EXPOSURE

- A. Around 11% of children 6 years and younger are regularly exposed to environmental tobacco smoke (ETS) in their homes. Parents/caregivers are responsible for 90% of this exposure.
- B. ETS exposure is higher, and asthma prevalence is more likely in households with low-income and low education levels.
- C. Children: Particularly vulnerable to the effects of ETS because they:
 - 1. Are still developing physically
 - 2. Have higher respiratory rates than adults
 - 3. Have little control over their indoor environments
- D. ETS Exposure: Has been associated with:
 - 1. Asthma
 - 2. Sudden infant death syndrome
 - 3. Respiratory tract infections
 - 4. Ear infections
- E. Efforts to Reduce ETS
 - 1. Smoking cessation programs
 - 2. Reducing ETS in the home is critical because the home is primarily where children are exposed to ETS.
 - a. Caregivers should smoke outside the home.
 - b. Smoke can cling to clothing, and clothing should be changed before handling a child.

- c. Choose child care facilities that are nonsmoking inside and out.
 - d. Do not allow anyone to smoke in the vehicles children ride in.
 - e. Choose restaurants and businesses that are smoke free. “No smoking” sections do not protect children from ETS.
- F. E-cigarettes
 - 1. E-cigarettes have become the most commonly used tobacco product in children, teens, and young adults.
 - 2. Contain addictive nicotine and toxic chemicals such as lead, diacetyl, and nickel
 - 3. Advertising and unique flavors attract youth, posing a significant health risk to the next generation.
 - 4. A small amount of liquid nicotine can be fatal to a child if spilled on skin or ingested. Adults using these products should abide by the following recommendations:
 - a. Lock up liquid nicotine refills and keep them out of the child’s reach.
 - b. Purchase refills with child-resistant packaging.
 - c. Never place the product in food or drink containers.
 - 5. Pediatric pharmacists should raise awareness of the increased use of e-cigarettes, potential health effects, and poison prevention strategies.

XII. BIOTERRORISM

- A. Children have been identified as a specific vulnerable population to bioterrorism for many reasons:
 - 1. Proximity to ground
 - 2. Increased respiratory rates
 - 3. Provider unfamiliarity with pediatric dosing of medications
 - 4. Lack of knowledge or inability to flee danger
 - 5. Inadequate reserve of pediatric-dosed antidotes and vaccines
 - 6. Less blood volume/physiologic reserve
 - 7. Thinner skin
 - 8. Increased body surface area/mass ratio
 - 9. Developmental immaturity
 - 10. Increased head size compared with body
- B. Pharmacists are well positioned to participate in emergency response activities, including drug distribution and dispensing, patient education, educating and training other health care providers, planning and preparation efforts, and vaccine administration.

XIII. CHALLENGES OF PEDIATRIC PHARMACY PRACTICE

- A. Improving Adherence in the Pediatric Population
 - 1. Medication adherence in children is 11%–93%.
 - 2. At least one-third of all patients do not complete relatively short-term treatment regimens.
 - 3. Key factors to nonadherence include:
 - a. Social and economic issues
 - b. Health literacy
 - c. Patient belief systems
 - d. Patient education

- e. Acceptability and palatability of medication. Children often identify difficulty in swallowing pills as a key barrier to taking oral medications.
- f. Adverse effects of medication
- 4. When addressing nonadherence in the pediatric population, both the patient's and the caregiver's issues must be dealt with.
- 5. Chief among the many issues to address with adherence include patient and/or caregiver's understanding of the medication regimen, acceptance of the need for adherence, and health care provider continuity in response to questions that may arise during treatment.
- 6. Taking the time to explain the treatment plan and the importance of adherence to both patients and their caregivers, getting feedback on their understanding and circumstances, is essential to improving adherence.
- 7. The caregiving environment can also largely affect adherence.
 - a. Often, pediatric patients are accompanied by one of potentially several caregivers who share information and coordinate the treatment regimen, which can lead to miscommunication and misunderstandings.
 - b. Children may also be transported across different sites during a week or a day, thus complicating the availability of medication, coordination of treatment, and desire or ability to adhere.
- 8. Strategies to improve adherence include:
 - a. Asking about difficulties in administering medications to the child currently or in the past. Be specific, ask about tablet size/swallowing and taste problems, and ask what was done to the medication (crush/dilute/flavor).
 - b. Trying to avoid regimens that require administration during school activities
 - c. Negotiating treatment regimens with the patient and family to devise a regimen the child is most likely to adhere to
 - d. Using the simplest effective regimen available
 - e. Using technology and devices (i.e., applications on smartphones) to enhance adherence
 - f. Improving communication between the care team and the patient and/or family with outreaches (telephone, e-mail, or text) to address any issues or concerns
- 9. Administering medications in the school setting – American Academy of Pediatrics recommends considering the following when prescribing medications for school-aged children and adolescents:
 - a. Prescribe medications that require administration at school only when necessary.
 - b. Learn about local school nursing services, medication policies, and self-administration procedures.
 - c. Write specific, clear, and detailed instructions on dated, standardized school medication forms. Carefully consider your patient's ability to self-carry/self-administer emergency medications when you are writing instructions.
- 10. Access to medications and public health resources
 - a. Children's Health Insurance Program (CHIP) – CHIP provides health insurance to almost 8 million children in families who have incomes too high to qualify for Medicaid but who cannot afford private insurance.
 - i. Like Medicaid, CHIP is administered by the states but is jointly funded by the federal and state government.
 - ii. States can design their CHIP program in one of three ways:
 - (a) Medicaid expansion
 - (b) Separate CHIP
 - (c) Combination of the two approaches
 - b. Prescription drug coverage is an optional benefit under the CHIP plan, but all states currently provide coverage for outpatient prescription drugs.
 - c. In 2018, CHIP funding was extended through September 2027.

Patient Case

5. J.D. is a 7-year-old boy with a history of mild persistent asthma treated with fluticasone hydrofluoroalkane 44 mcg 2 puffs twice daily. He has just been given a diagnosis of attention-deficit/hyperactivity disorder. Which treatment regimen is ideal to initiate for his disorder?
- A. Methylphenidate immediate release 5 mg orally at 7 a.m. and noon daily.
 - B. Methylphenidate extended release 18 mg orally at 7 a.m. daily.
 - C. Atomoxetine 100 mg orally at 7 a.m. daily.
 - D. Transdermal methylphenidate 15-mg patch applied daily.

B. Assistance Through the Cystic Fibrosis Foundation

- 1. Cystic Fibrosis Foundation *Compass* provides free, personalized case manager services to assist with insurance, financial, and legal issues.
- 2. Services are available to those with cystic fibrosis, their family, and their care team.
- 3. www.cff.org/support#insurance-finances-legal or 844-COMPASS

C. Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)

- 1. WIC provides federal grants to states for supplemental foods and health care to women, infants, and children who are at nutritional risk.
- 2. Target population is low income, nutritionally at risk:
 - a. Pregnant women (through pregnancy and up to 6 weeks after birth or after pregnancy ends)
 - b. Breastfeeding women (up to infant's first birthday)
 - c. Non-breastfeeding postpartum women (up to 6 months after the birth of an infant or after pregnancy ends)
 - d. Infants (up to first birthday). WIC serves 53% of all infants born in the United States.
 - e. Children up to their fifth birthday
- 3. The following benefits are provided to WIC participants:
 - a. Supplemental nutritious foods
 - b. Nutrition education and counseling at WIC clinics
 - c. Screening and referrals to other health, welfare, and social services

D. HealthWell Pediatric Assistance Fund

- 1. Fund developed to assist children 18 years and younger living with a chronic or life-altering condition that their families find difficult to treat because of cost
- 2. Provide financial assistance to families so that their children can start or continue critical medical treatments, regardless of disease type or condition
- 3. www.healthwellfoundation.org/fund/pediatric-assistance/ or (800) 675-8416

E. Healing the Children

- 1. Helps children throughout the world receive medical care that would otherwise be unavailable to them because of a lack of medical and financial resources or health insurance
- 2. Twelve chapters located across the United States work together to provide services to children, both domestically and abroad.
- 3. www.healingthechildren.org or (509) 327-4281

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ANSWERS AND EXPLANATIONS FOR PATIENT CASES**1. Answer: D**

Although all the options apply to chloramphenicol use, the most worrisome aspect of using this drug in the neonatal population is the known severe adverse event of gray baby syndrome, which can be associated with death (Answer D is correct; Answers A–C are incorrect). Moreover, it is best to provide the provider with the detail to support why benefit is not worth the risk (Answer C is incorrect).

2. Answer: C

The FDA issued information recommending against tramadol use in children 12–18 years of age who have obesity because of an increased risk of slowed or difficult breathing. According to the Centers for Disease Control and Prevention, obesity is a BMI at or above the 95th percentile for young people of the same age and sex (Answer C is correct). Tramadol is contraindicated for treating pain in children younger than 12 years (Answer A is incorrect). Although tramadol is not contraindicated in children older than 12 years who did not have a T and A procedure, this is not the best answer because the patient has obesity (Answer B is incorrect). Hydrocodone-containing products do not have more safety and efficacy data in pediatric patients. In fact, in 2018, the FDA issued label changes to prescription cough and cold medications containing hydrocodone because of the risks associated with its use in children younger than 18 years (Answer D is incorrect).

3. Answer: A

Poison Control has the best resources to advise this mother on the next steps regarding her child's ingestion of glue (Answer A is correct). Syrup of ipecac is no longer recommended because it lacks evidence for improved outcomes (Answer C is incorrect). Many ingestions can be managed in the home setting with the assistance of Poison Control (Answer B is incorrect). Consequently, an emergency department visit and a pediatrician's advice may not be needed (Answer D is incorrect).

4. Answer: C

The best strategy for addressing parents' concerns regarding immunizations is to establish open, ongoing, nonconfrontational dialogue and to target education to the caregiver's specific concerns (Answer C is correct). Although the thimerosal dose contained in vaccine

products is very low, Answer A is not the best answer because the dialogue does not promote an open, nonconfrontational conversation (Answer A is incorrect). As mentioned previously, some multidose vaccine vials do contain a small amount of thimerosal (Answer B is incorrect). Providing general information regarding the importance of vaccinations is not as effective as addressing the parent's specific concern (Answer D is incorrect).

5. Answer: B

Once-daily extended-release methylphenidate (methylphenidate ER) is better than immediate-release methylphenidate because this is a school-aged child, and medications that must be administered at school complicate the treatment plan. In addition, a once-daily regimen is more likely to optimize adherence (Answer B is correct; Answer A is incorrect). Atomoxetine 100 mg (Answer C) and transdermal methylphenidate 15 mg (Answer D) are not starting doses for patients who are naive to stimulant therapy.

ANSWERS AND EXPLANATIONS FOR SELF-ASSESSMENT QUESTIONS

1. Answer: D

Although Answers A–C apply to the challenges of using medications in pediatric patients, the inherent challenge of the lack of published data in pediatric patients (Answer D), when combined with the lack of FDA-approved indications in pediatric patients, summarizes the overall complexity of medication use in this population.

2. Answer: D

The Kefauver-Harris Drug Amendment required the demonstrated safety and efficacy of drugs and biologics for human use but excluded the pediatric population (Answer A is incorrect). The Orphan Drug Act provided incentives for developing orphan drugs (Answer B is incorrect). Answer C is incorrect because BPCA made pediatric studies voluntary in order to add a financial incentive to encourage pediatric drug and biologic research. Answer D is correct because PREA allowed the FDA to require pediatric studies only for the same indications as approved for adults.

3. Answer: D

Both PREA and BPCA cover biologics (Answer A is incorrect). For PREA, conducting pediatric studies is mandatory, whereas for BPCA, it is voluntary (Answer B is incorrect). Only under BPCA may indications be expanded (Answer C is incorrect). For both PREA and BPCA, the goal is to establish appropriate use and labeling in pediatric patients (Answer D is correct).

4. Answer: C

Unlike PREA, which states that orphan drugs are exempt from study, BPCA states that orphan indication studies can be requested (Answer A is incorrect). Asthma as a disease state does not meet the definition of a rare disease, even if the indication is not studied in the pediatric population (Answer B is incorrect). The Orphan Drug Act requires accelerated drug development for rare pediatric diseases (Answer D is incorrect). Because rare disease states seldom occur in children, drug manufacturers rely on the Orphan Drug Act for incentive to study the often cost-prohibitive drugs associated with such disease states (Answer C is correct).

5. Answer: A

The *AHFS Drug Information* (book) is a reference best known for providing both on-label and off-label uses of drugs (Answer A is correct; Answers B–D are incorrect).

6. Answer: B

Explaining that the supply of alprostadil vials is being conserved because there are no therapeutic alternatives for this indication is the best choice because it informs the provider of why drug conservation is essential (Answer B is correct; Answers A, C, and D are incorrect).

7. Answer: A

The purpose of the National Institute for Children's Health Quality is to improve child health by improving the systems of children's health care (Answer A is correct). The role of PREA is to allow the FDA to require research in pediatric patients (Answer B is incorrect). The role of BPCA is to encourage drug manufacturers to conduct pediatric research by providing incentives (Answer C is incorrect). Finally, the role of the FDA Office of Pediatric Therapeutics is to improve child health by ensuring access for children to innovative, safe, and effective medical products (Answer D is incorrect).

8. Answer: C

No data support the suggestion that an interaction exists between intramuscular ceftriaxone-containing products and intravenous calcium-containing products (Answer C is correct; Answer A is incorrect). Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates younger than 28 days, but this patient is 18 months of age (Answer D is incorrect). Azithromycin is a less-than-ideal treatment option because of its lack of activity against most *Haemophilus influenzae* strains and increasing resistance to pneumococcal isolates (Answer B is incorrect).

9. Answer: B

E-cigarettes have become the most commonly used tobacco product in children, teens, and young adults (Answer B is correct). Parents' use of e-cigarettes gives children easier access and places them at risk of toxicity from accidental ingestion of liquid nicotine (Answer A is incorrect). Aside from nicotine, e-cigarettes contain toxic chemicals, including lead, diacetyl, and nickel (Answer C is incorrect). Children are particularly vulnerable to the effects of ETS because they are still physically developing, have a higher respiratory rate than adults, and have little control over their environment.

10. Answer: D

Studies have shown that medium-dose sildenafil produces favorable results in pediatric patients with PAH, whereas low doses have had no benefit, and high doses have resulted in increased mortality (Answer D is correct). The FDA recommendations and researchers differ in opinion on sildenafil use in pediatric patients (Answer C is incorrect). The FDA recommends against using sildenafil, but authors of the STARTS-2 study support the use of medium-dose sildenafil (Answer B is incorrect). More information is needed to further address the role of sildenafil for PAH in the pediatric population (Answer A is incorrect).

IMMUNOLOGY

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Learning Objectives

1. Develop a therapeutic regimen for patients with immunologic conditions.
2. Design a plan to monitor the safety and efficacy of a therapeutic regimen in patients with immunologic conditions.
3. Develop a therapeutic regimen to prevent acquisition of infection-related immunologic diseases.
4. Manage allergic hypersensitivity reactions effectively.
5. Develop an individualized immunization plan for a pediatric patient.

Abbreviations in This Chapter

ACIP	Advisory Committee on Immunization Practices
ACR	American College of Rheumatology
ANA	Antinuclear antibody
ART	Antiretroviral therapy
CMV	Cytomegalovirus
DMARD	Disease-modifying antirheumatic drug
DTaP	Diphtheria, tetanus, acellular pertussis
GAS	Group A <i>Streptococcus</i>
HCT	Hematopoietic cell transplantation
Hib	<i>Haemophilus influenzae</i> type b
HPV	Human papillomavirus
IIV	Inactivated influenza vaccine
INSTI	Integrase strand transfer inhibitor
JIA	Juvenile idiopathic arthritis
LAIV	Live attenuated influenza vaccine
LFT	Liver function test
LN	Lupus nephritis
MAC	<i>Mycobacterium avium</i> complex
MMR	Measles, mumps, and rubella
NRTI	Nucleoside reverse transcriptase inhibitor
OI	Opportunistic infection
PI	Protease inhibitor
PJP	<i>Pneumocystis jiroveci</i> pneumonia
SCID	Severe combined immunodeficiency
SLE	Systemic lupus erythematosus
STI	Sexually transmitted infection
Tdap	Tetanus, diphtheria, acellular pertussis
TNF	Tumor necrosis factor

Self-Assessment Questions

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

1. A 7-year-old previously healthy boy presents with 6 weeks of bilateral lower-extremity edema, fatigue, decreased appetite, and lymphadenopathy. He also has hypertension, hematuria, proteinuria, positive antinuclear antibodies (ANAs), and anti-DNA antibodies. He has a kidney biopsy and receives a diagnosis of class IV lupus nephritis (LN). Which immunosuppressive regimen would be most appropriate to initiate first?
 - A. Methylprednisolone and mycophenolate mofetil.
 - B. Methylprednisolone and losartan.
 - C. Methylprednisolone plus mycophenolate mofetil plus azathioprine.
 - D. Methylprednisolone plus rituximab.
2. A 16-year-old female adolescent (weight 40 kg) presents with a history of acute rheumatic fever complicated by rheumatic heart disease. She recently emigrated from Polynesia with her parents. Her parents report that she was first given a diagnosis of acute rheumatic fever about 3 years ago and was taking medications but stopped them once her symptoms resolved. She has no symptoms of arthritis; her Doppler echocardiography reveals mild rheumatic mitral regurgitation. The medical records from her treatment outside the United States are unavailable. Her parents report no allergies to medications. Which treatment plan is most appropriate to initiate at this time?
 - A. Aspirin 3 g orally once daily.
 - B. Prednisone 5 mg orally once daily.
 - C. Benzathine penicillin G 1,200,000 units intramuscularly every 4 weeks.
 - D. Amoxicillin 1 g orally once daily.

3. The primary care physician for a 14-year-old male adolescent with cystic fibrosis and anaphylaxis to ceftazidime wishes to have the patient desensitized to ceftazidime in order to treat a cystic fibrosis-related pulmonary exacerbation secondary to a multidrug-resistant *Pseudomonas aeruginosa*. Which statement regarding desensitization to ceftazidime is most accurate?
 - A. If desensitization is successful, the patient will be able to tolerate ceftazidime for the rest of his life.
 - B. If desensitization is successful, the patient will only temporarily be able to tolerate ceftazidime.
 - C. Desensitization is likely to be unsuccessful because breakthrough reactions are common during the procedure.
 - D. Desensitization would not be recommended for an acutely ill child because it would take weeks to months to become fully desensitized to ceftazidime.
4. A 2-year-old girl was recently given a diagnosis of egg allergy. The reaction included angioedema and hives; however, the patient can tolerate eggs in baked goods. The patient is not up to date on her vaccinations, and her primary care physician wonders whether she can receive the measles, mumps, and rubella (MMR) and influenza vaccines because both vaccines contain an egg protein. Which would be the best recommendation?
 - A. Recommend that a physician with expertise in allergy management administer both vaccines.
 - B. Advise against administering either the MMR or the flu vaccine.
 - C. Recommend administering both the MMR and the influenza vaccine as usual.
 - D. Recommend administering the MMR vaccine but not the influenza vaccine.
5. The parents of a 2-year-old girl wish to have their child tested for food allergies. The patient's 5-year-old brother is severely allergic to eggs (reaction noted to be anaphylaxis), and the parents are afraid of introducing eggs to her diet before checking for egg allergy. Which recommendation is most appropriate?
 - A. Recommend a skin prick test to check for egg allergy.
 - B. Recommend measuring immunoglobulin (Ig) E serum concentrations.
 - C. Recommend oral egg immunotherapy.
 - D. Do not recommend egg allergy testing at this time.
6. A 4-month-old boy is given a diagnosis of X-linked severe combined immunodeficiency (SCID) through the newborn screening program. Which best depicts a first-line treatment strategy for managing this disorder?
 - A. Gene therapy.
 - B. Hematopoietic cell transplantation (HCT).
 - C. IgG replacement.
 - D. Antimicrobial prophylaxis.
7. A 15-year-old male adolescent has a new prescription for minocycline 100 mg orally twice daily for 6 weeks for an acne outbreak. However, he hesitates to take the medication because he read in the package insert that it can cause lupus, and his aunt recently died of complications of lupus. Which recommendation is most appropriate?
 - A. Agree with the patient, and recommend talking to the prescribing physician about alternatives.
 - B. Explain to the patient that he is at low risk because minocycline-induced lupus usually develops in individuals who have been taking minocycline for years.
 - C. Explain to the patient that he is at low risk because males are significantly less likely to develop lupus than females.
 - D. Recommend to the patient that he undergo laboratory testing for antibodies commonly associated with lupus to have his risk of disease assessed before taking minocycline.

8. A 17-year-old male adolescent presents to the ED after having unprotected sexual intercourse with another male known to be HIV positive. The patient states that the event occurred 24 hours ago. He also reports testing positive for gonorrhea and negative for HIV about 6 months ago. Which treatment would be best to recommend?
- A. Emtricitabine/tenofovir 1 tablet orally once daily and raltegravir 400 mg orally twice daily for 4 weeks.
 - B. Emtricitabine/tenofovir 1 tablet orally once daily and abacavir 600 mg orally once daily for 4 weeks.
 - C. Emtricitabine/tenofovir 1 tablet orally once daily and lamivudine 300 mg orally once daily for 4 weeks.
 - D. Emtricitabine/tenofovir 1 tablet orally once daily and zidovudine 300 mg orally once daily for 4 weeks.
9. A 37 weeks' gestation newborn (weight 3.1 kg) is delivered to a mother who is HIV positive (CD4 count 424 cells/mm³, viral load less than 20 copies/mL). The mother received prenatal care and was adherent to her antiretroviral medications. Which antiretroviral regimen is most appropriate to prevent transmission of HIV to the infant?
- A. No antiretroviral prophylaxis is needed because the mother's viral load is undetectable.
 - B. Start zidovudine 12.4 mg orally twice daily for 4 weeks.
 - C. Start zidovudine 12.4 mg orally twice daily for 6 weeks and nevirapine 12 mg orally for three doses on days 1, 3, and 7.
 - D. Start zidovudine 12.4 mg orally twice daily and nevirapine 12 mg orally every 48 hours for 6 weeks.
10. An 8-year-old boy is being newly initiated on topical pimecrolimus 1% for moderate to severe atopic dermatitis. Which counseling point is most important to mention to the parents regarding the medication before dispensing it?
- A. Can cause skin atrophy.
 - B. Can cause stinging/burning.
 - C. Should only be used during flares; stop applying it once improvement is noted.
 - D. Will require laboratory monitoring of drug concentrations.
11. A 14-year-old male adolescent is being seen in the rheumatology clinic after being unwell for about 3 months. He initially presented with diffuse arthralgias but subsequently developed a temperature of up to 102.3°F. He misses several days of school each week. On physical examination, he had a systemic rash, diffuse lymphadenopathy, and oligoarthritis involving both wrists and elbows. After a thorough workup, he was given a diagnosis of systemic juvenile idiopathic arthritis (JIA) and treated with naproxen 500 mg orally twice daily. His symptoms and inflammatory markers have not improved during a follow-up. Which treatment is most appropriate to recommend at this time?
- A. Anakinra.
 - B. Etanercept.
 - C. Abatacept.
 - D. Rituximab.
12. A 10-year-old girl with polyarticular JIA presents to the clinic with joint pain. Her current therapy consists of methotrexate and naproxen, and the rheumatologist is considering initiating adalimumab. Which infection would the patient best be screened for before adalimumab is initiated?
- A. Methicillin-resistant *Staphylococcus aureus*.
 - B. Tuberculosis.
 - C. Cytomegalovirus (CMV).
 - D. Hepatitis C.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.3, 1.4, 1.5, 1.6
2. Domain 4: Public Health and Patient Advocacy; Task(s): 4.1, 4.3

I. ECZEMA/ATOPIC DERMATITIS

- A. Atopic Dermatitis Definition and Diagnosis
 - 1. Chronic pruritic inflammatory disease with a relapsing course
 - 2. Atopic dermatitis is the most common (but not the only) type of eczema.
 - 3. Estimated prevalence in children is 10%–20%.
 - 4. Usually presents within the first year of life
- B. Pathophysiology
 - 1. Defective epidermal barrier function – Skin water loss
 - 2. Atopic skin inflammation – Extravasation of inflammatory cytokines into skin
- C. Diagnosis – Based on clinical features
 - 1. Pruritus
 - 2. Eczema
 - a. Chronic or relapsing history
 - b. Typical morphology and age-specific pattern
 - i. Facial, neck, and extensor involvement in infants and children
 - ii. Current or previous flexural lesions in any age group
 - iii. Sparing of the groin and axillary regions
- D. Comorbidities
 - 1. Higher risk of developing other atopic diseases (food allergies, asthma, allergic rhinitis)
 - 2. Higher risk of infection because of impaired skin barrier
- E. Symptoms: Pruritus, erythema, edema, xerosis, erosions/excoriations, crusting, lichenification
- F. Goals of Therapy
 - 1. To decrease inflammation and restore integrity of the skin barrier
 - 2. To provide relief from itching
- G. Nonpharmacologic Therapy
 - 1. Moisturizers are recommended for all patients and should be applied throughout the day.
 - a. Lessen symptoms and prescription anti-inflammatory drug use, increase hydration
 - b. Emollients (glycol, glyceryl stearate, soy sterols) lubricate/soften skin; occlusive agents (petrolatum, dimethicone, mineral oil) retard water evaporation; humectants (glycerol, lactic acid, urea) attract/hold water.
 - 2. Bathing
 - a. Non-soap cleaners that are low-neutral pH, hypoallergenic, and fragrance free
 - b. A recent study showed that twice-daily soaking baths for 10 minutes or less, followed by immediate application of an occlusive moisturizer, were effective for acute management of atopic dermatitis (J Allergy Clin Immunol Pract 2020;8:1014-21).
 - 3. Wet-wrap therapy can help reduce the severity of acute flares.
 - a. Increased penetration of topical agent, decreased water loss, prevention of scratching
 - b. Apply topical steroid, then wet layer, and then dry layer (gauze, cotton pajamas/socks). Usually applied daily for several hours (depending on patient tolerance) and continued for several days

4. Other

- a. Cover the affected skin to protect it from scratching (long sleeves/pants, bandages); keep child's nails trimmed
- b. Avoid clothing that's rough, too tight, or scratchy to decrease irritation
- c. Consider humidifier if living in hot/dry climate as it may worsen itching and flaking

H. Pharmacologic Therapy (Table 1)

1. Topical steroids

- a. Mechanism of action: Anti-inflammatory by several mechanisms such as decreased synthesis of interleukins and several other proinflammatory cytokines, suppressed cell-mediated immunity, reduced complement synthesis, and decreased production and activity of leukocytes
- b. Usually considered first-line therapy; largely used for flare-ups but can be used as "maintenance" therapy (once or twice weekly) to prevent relapse
- c. Potency
 - i. Grouped into seven classes from lowest (VII) to very high (I) potency
 - ii. Depends on both drug concentration and vehicle used. In general, ointments and gels are more potent than lotions and creams.
- d. Pharmacokinetics: The amount of corticosteroid absorbed from the skin depends on the intrinsic properties of the drug itself, vehicle used, duration of exposure, and surface area and condition of the skin to which it is applied. In general, absorption will be enhanced by increased skin temperature, hydration, application to inflamed or denuded skin, intertriginous areas (e.g., eyelids, groin, axilla), or skin surfaces with a thin stratum corneum layer (e.g., face, scrotum). Palms, soles, and crusted surfaces are less permeable.
- e. Usually recommended if lesions have not responded to skin care and moisturizers alone
- f. A variety of strengths and formulations exist (Table 2), but they are usually applied once or twice daily for 3–7 days for acute flares.
- g. Maintenance therapy is usually considered in patients with frequent outbreaks involving the same body sites.
- h. Adverse effects: Skin atrophy (face and intertriginous area are particularly susceptible); systemic adverse effects with high-potency agents, although the risk of HPA (hypothalamic-pituitary-adrenal) axis suppression is low

2. Topical calcineurin inhibitors (TCIs)

- a. Mechanism of action: Inhibition of cytokine production and T-cell proliferation by calcineurin inhibition
- b. Usually considered second-line therapy but can be considered first line for sensitive areas such as the face and intertriginous area
- c. Tacrolimus (Protopic) ointment 0.03% and 0.1% and pimecrolimus (Elidel) cream 1%
 - i. Twice-daily dosing for acute treatment
 - ii. Two or three-times-weekly application for maintenance
 - iii. Not FDA label approved for children younger than 2 years, but has been used off-label
- d. Adverse effects: Local reactions (stinging, burning), malignancy (controversial); package insert recommends avoiding use during concomitant skin infection

3. Combination therapy (topical corticosteroids and topical calcineurin inhibitors): Can be used concomitantly or sequentially

4. Topical phosphodiesterase type 4 inhibitors

- a. Mechanism of action: Suppression of proinflammatory cytokines by inhibiting the degradation of cyclic adenosine monophosphate to adenosine monophosphate

- b. Crisaborole ointment 2% (Eucrisa)
 - i. FDA approved in 2016 for mild to moderate atopic dermatitis in children 3 months and older
 - ii. Twice-daily dosing
 - iii. Usually considered second-line therapy
 - iv. Usually well tolerated; reports of hypersensitivity reactions (hives, itching, swelling, redness)
 5. Systemic biologic agents
 - a. Mechanism of action: Monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 by binding to the shared alpha subunit of the IL-4 receptor. This results in inhibition of helper T cell 2 activation and inflammatory mediators and up-regulation of epidermal barrier and structural proteins
 - b. Dupilumab (Dupixent)
 - i. FDA approved for children 6 years and older
 - ii. Dosing:
 - (a) 15–29 kg: 600 mg once, then 300 mg subcutaneously every 4 weeks
 - (b) 30–59 kg: 400 mg once, then 200 mg subcutaneously every other week
 - (c) 60 kg and greater: 600 mg once, then 300 mg subcutaneously every other week
 - iii. Common adverse effects: Injection-site reactions, conjunctivitis, oral herpes simplex infections
 - iv. Concurrent administration of live vaccines not recommended
 - v. Recommended for long-term control of severe atopic dermatitis, not acute flares
 6. Systemic antihistamines may be used to decrease itching (commonly given before bedtime). Topical antihistamines offer little benefit.
 7. Other therapies (third line) for severe/refractory atopic dermatitis
 - a. Azathioprine (Imuran)
 - b. Cyclosporine (Gengraf, Sandimmune, Neoral)
 - c. Methotrexate (Trexall)
 - d. Mycophenolate mofetil (CellCept)
 - e. Systemic corticosteroids should be avoided, if possible, because of their adverse effects and negative effects on growth.

Table 1. Pharmacologic Management of Atopic Dermatitis

	Acute Flare	Maintenance Therapy
Mild	Low-medium potency TCS twice daily Alternative: TCI, crisaborole	Skin care (liberal use of moisturizers, daily baths followed by moisturizer)
Moderate	Medium-high potency TCS twice daily for 3–7 days Alternative: TCI, crisaborole	Low-potency TCS once or twice daily (including face), or Medium-potency TCS once or twice daily (excluding face), or TCI once or twice daily, or Crisaborole twice daily
Severe	Medium-high potency TCS twice daily for 3–7 days Alternative: TCI, crisaborole Referral to pediatric specialist if no resolution after 7 days	Dupilumab Systemic immunosuppressants Referral to pediatric specialist

TCI = topical calcineurin inhibitor; TCS = topical corticosteroid.

Table 2. Topical Steroid Formulations and Relative Potencies

Generic Name	Brand Name	Strength (%)	Dosage Form(s)
I. Very high potency			
Augmented betamethasone dipropionate	Diprolene	0.05	O
Clobetasol propionate	Clobex, Olux, Temovate, Temovate E	0.05	O, C, F
Diflorasone diacetate	ApexiCon	0.05	O
Halobetasol propionate	Ultravate	0.05	O, C
II. High potency			
Amcinonide	—	0.1	O, C, L
Augmented betamethasone dipropionate	Diprolene AF	0.05	C
Betamethasone dipropionate	Betanate	0.05	O, C, F
Desoximetasone	Topicort	0.25 (C, O), 0.05 (G)	O, C, G
Diflorasone diacetate	Psorcon, ApexiCon E	0.05	C
Fluocinonide	Lidex	0.05	O, C, G
Halcinonide	Halog	0.1	O, C
Mometasone furoate	Elocon	0.1	O
Triamcinolone acetonide	Cinalog	0.5	O, C
III. Upper medium potency			
Fluticasone propionate	Cutivate	0.005	O
Betamethasone valerate	Luxiq	0.12	F
IV. Medium potency			
Flurandrenolide	Cordran	0.05	O, C
Mometasone furoate	Elocon	0.1	C, L
Triamcinolone acetonide	Kenalog	0.1	O, C
Fluocinolone acetonide	Synalar	0.025	O, C
Desoximetasone	Topicort LP	0.05	O, C
Clocortolone pivalate	Cloderm	0.1	C
Fluticasone propionate	Cutivate	0.05	C, L
V. Lower medium potency			
Hydrocortisone butyrate	Locoid	0.1	O
Hydrocortisone probutate	Pandel	0.1	C
Hydrocortisone valerate	Westcort	0.2	O, C
Prednicarbate	Dermatop	0.1	C
VI. Low potency			
Alclometasone dipropionate	Aclovate	0.05	O, C
Desonide	Desonate, DesOwen, Verdeso	0.05	O, C, G, F
Fluocinolone acetonide	Synalar, Derma-Smoothe	0.01	C
VII. Lowest potency			
Hydrocortisone (acetate)	—	0.5–2.5	O, C, L

C = cream; F = foam; G = gel; L = lotion; O = ointment.

Patient Cases

1. A 9-month-old boy is brought to the pediatric clinic by his parents for atopic dermatitis diagnosed at 3 months of age. Physical examination reveals thick, excoriated, hyperpigmented eczematous plaques on the forearms, wrists, and lower extremities. Past treatments for this problem include OTC hydrocortisone 1% cream. His mother reports that she has been using the creams as needed with mild improvement. In addition to daily moisturizing, which regimen would be most appropriate to treat this patient's acute flare?
 - A. Hydrocortisone 0.5% cream applied to the affected areas twice daily.
 - B. Clobetasol 0.05% ointment applied to the affected areas twice daily.
 - C. Triamcinolone acetonide 0.1% ointment applied to the affected areas twice daily.
 - D. Crisaborole ointment 2% applied to the affected areas twice daily.
2. A 2-year-old boy is newly initiated on hydrocortisone butyrate ointment for an acute flare of atopic dermatitis located on his cheeks, hands, and elbows. Which adverse effect would be most appropriate to mention to the primary caregiver when using this medication?
 - A. Increased risk of infection when using this medication.
 - B. Increased redness and itching when using this medication.
 - C. Increased risk of skin atrophy, particularly on face.
 - D. Increased risk of cancer when using this medication.

II. JUVENILE IDIOPATHIC ARTHRITIS

- A. Definition/Epidemiology
 1. Arthritis of unknown origin that begins before the 16th birthday and persists for at least 6 weeks
 2. Prevalence – About 1 in 1000
- B. Classification According to ILAR (International League of Associations for Rheumatology):
 1. Systemic arthritis (10%–20% of all cases): Fever of at least 2 weeks' duration (may follow a quotidian pattern) and arthritis in one or more joints, plus one of the following: erythematous rash, generalized lymph node enlargement, hepatomegaly and/or splenomegaly, serositis
 2. Oligoarthritis (50%–60% of all cases): Arthritis affecting four joints or fewer during the first 6 months of the disease. Can be persistent (affecting four joints or fewer after 6 months) or extended (affecting five or more joints after 6 months)
 3. Polyarthritis (25%–40% of all cases): Arthritis affecting five or more joints during the first 6 months of the disease; can be rheumatoid factor positive or negative
 4. Psoriatic arthritis (2%–15% of all cases): Arthritis and psoriasis or arthritis and at least two of the following:
 - a. Dactylitis
 - b. Nail pitting or onycholysis
 - c. Psoriasis in a first-degree relative
 5. Enthesitis-related arthritis (1%–7%): Arthritis **and** enthesitis (inflammation of attachment points of ligaments or tendons to the bone) **or** arthritis or enthesitis with at least two of the following:
 - a. Presence/history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain and *HLA-B27* positive
 - b. Onset of arthritis in a male older than 6 years

- c. Acute (symptomatic) anterior uveitis
 - d. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, or acute anterior uveitis in a first-degree relative
- 6. Undifferentiated arthritis: Arthritis that fulfills the criteria in no category or in two or more of the previous categories
- C. Pathogenesis
 - 1. Increased amount of synovial fluid
 - 2. Expansion of inflamed synovial tissue
 - 3. Inflammatory cell infiltration into the synovium – Degradation of the collagen and proteoglycan matrix of the articular cartilage, activation of osteoclasts with resulting bone demineralization and bone erosions
- D. Clinical Manifestations
 - 1. Arthritis – Swelling, warmth, pain, loss of function in the affected joints
 - 2. Systemic symptoms (only in patients with systemic disease)
 - a. Most common: Fever, rash
 - b. Others: Lymphadenopathy, splenomegaly, pericardial effusion, myocarditis, anemia, macrophage activation syndrome
- E. Complications/Comorbidities
 - 1. Uveitis (most common with oligoarthritis): Can lead to cataracts, glaucoma, macular edema, synechiae. Depending on risk (age at arthritis onset and presence of ANAs), patients should be screened every 3–12 months.
 - 2. Osteoporosis
 - 3. Growth retardation
 - 4. Leg length discrepancy
 - 5. Macrophage activation syndrome (in systemic disease): Excessive inflammation and tissue destruction caused by abnormal immune activation, rare but life threatening
 - 6. Temporomandibular joint: Can lead to dysmorphic facial features, pain, dental problems, difficulty chewing/swallowing
- F. Laboratory Findings: No laboratory findings are specific for the diagnosis of JIA. They are merely suggestive and need to be used in conjunction with clinical presentation.
 - 1. Elevated erythrocyte sedimentation rate, CRP, WBC, Plt, D-dimer, ferritin, liver function tests (LFTs)
 - 2. May have positive ANA in oligo- or polyarticular disease (not systemic)
 - 3. May have positive rheumatoid factor, mainly in polyarticular disease. ANA and RF confer risk of additional complications/disease activity.
- G. Treatment (Table 3)
 - 1. Intra-articular steroids
 - a. Mechanism of action: Anti-inflammatory by several pathways (described in the Atopic Dermatitis section)
 - b. Usually used only if a few joints are affected and as adjunctive therapy
 - c. Triamcinolone hexacetonide (Aristospan) is preferred to triamcinolone acetonide (Kenalog) because of more complete and longer duration of clinical response. Aristospan is currently unavailable in the United States but can be obtained through the FDA import process.
 - d. Mean duration of effect about 12 months, sometimes 24 months
 - e. Adverse effects: Skin/fat atrophy (most common), infection; young children will require sedation

2. Systemic steroids
 - a. Use should be minimized as much as possible. Usually reserved for patients with acute systemic symptoms and/or as bridge therapy in those with moderate to severe disease activity
 - b. Different dosing regimens exist, depending on severity on presentation (e.g., prednisone 0.25–1 mg/kg [max 60 mg] orally once daily). Some clinicians use methylprednisolone pulse therapy 30 mg/kg (max 1 g) intravenously daily for 3 days first. Taper is usually initiated once clinical improvement is evident.
 - c. Adverse effects (short term): Hyperglycemia, leukocytosis, GI (gastritis, peptic ulcer disease, GI bleeding – risk further increased in combination with NSAIDs, immunosuppression, mood disturbances)
 - d. Adverse effects (long term): Growth suppression, osteoporosis/osteonecrosis, cataracts, weight gain, cardiovascular disease
3. NSAIDs
 - a. Mechanism of action: Anti-inflammatory by prostaglandin inhibition
 - b. Used as adjunctive therapy, not recommended as monotherapy
 - c. Similar efficacy between agents. Examples:
 - i. Naproxen (Aleve): 10–15 mg/kg/day orally in two divided doses
 - ii. Ibuprofen (Advil, Motrin): 30–40 mg/kg/day orally in three divided doses (max 2400 mg/day)
 - iii. Meloxicam (Mobic): 0.125–0.25 mg/kg orally daily (max 15 mg/day)
 - iv. Indomethacin (Indocin): 2–4 mg/kg/day orally in three divided doses (max 200 mg/day)
 - d. Adverse effects: GI upset, gastritis, renal toxicity
 - e. Monitoring: SCr, urinalysis, CBC, LFTs before initiation and then twice yearly for patients receiving long-term regimen (American College of Rheumatology [ACR] recommendations)
4. Nonbiologic disease-modifying antirheumatic drugs (DMARDs)
 - a. Methotrexate (Trexall)
 - i. Generally considered first-line therapy for patients with polyarthritis
 - ii. Dosing regimen: 10–15 mg/m²/week or 0.5–1 mg/kg/week (max 25 mg). Can be administered orally or subcutaneously – Subcutaneous route is preferred because it may cause fewer adverse effects and have better absorption. In addition, concurrent supplementation with folic acid 1 mg orally once daily is needed.
 - iii. Onset of action: 4–8 weeks
 - iv. Monitoring: CBC, LFTs, SCr before initiation and every 3–4 months with chronic use
 - v. Adverse effects: Diarrhea, stomatitis, hepatotoxicity, renal toxicity, rash, bone marrow suppression, immunosuppression
 - b. Leflunomide (Arava)
 - i. Mechanism of action: Inhibition of pyrimidine synthesis, immunomodulatory and anti-inflammatory effects by many pathways (inhibition of leukocyte adhesion to vascular endothelium, decreased synovial infiltration of lymphocytes, disrupted function of dendritic cells and memory T cells, decreased proinflammatory cytokines)
 - ii. Usually used in patients with polyarthritis or frequently relapsing oligoarthritis; second line for patients who cannot tolerate methotrexate
 - iii. Dose: 10 mg orally every other day (weight less than 20 kg), 10 mg orally daily (20–40 kg), 20 mg orally daily (weight greater than 40 kg)
 - iv. Onset of action: 2–4 months
 - v. Monitoring: CBC, LFTs, SCr every 3–4 months
 - vi. Adverse effects: Diarrhea, alopecia, respiratory infections
 - c. Others (for refractory disease)
 - i. Sulfasalazine (Azulfidine, Sulfazine)
 - ii. Hydroxychloroquine (Plaquenil)

5. Biologic DMARDs

a. “General guidelines”:

- i. CBC, LFTs, SCr before initiation and every 3–6 months thereafter
- ii. Tuberculosis screen before initiation and about once yearly
- iii. All can increase the risk of malignancy and infections.
- iv. Avoid live vaccinations while receiving biologic agents.
- v. Avoid combinations of biologic agents.
- vi. For polyarticular JIA, tumor necrosis factor (TNF) inhibitors are usually first line in patients with moderate to severe disease activity. TNF inhibitors are preferably used in combination with a DMARD (i.e., methotrexate). Figure 1 provides a treatment algorithm.
- vii. For systemic JIA, anti-IL-1 or anti-IL-6 agents are preferred.

b. TNF inhibitors

i. Safety concerns related to all TNF inhibitors

- (a) All have black box warnings for increased risk of serious infections (including hepatitis B reactivation) and malignancy.
- (b) Use with caution in patients with heart failure or decreased left ventricular function because worsening and new-onset heart failure have been reported. Infliximab has additional contraindications (see the text that follows).
- (c) A link between TNF inhibitors and demyelinating disease may exist.

ii. Adalimumab (Humira)

- (a) Type of biologic: 100% humanized monoclonal antibody
- (b) Usually used in patients with JIA without systemic features and uveitis
- (c) Dosing (FDA label approved for children 2 years and older)
 - (1) 10–14 kg: 10 mg subcutaneously every other week
 - (2) 15–29 kg: 20 mg subcutaneously every other week
 - (3) 30 kg or greater: 40 mg subcutaneously every other week
- (d) Onset of action within 2–4 weeks
- (e) Adverse effects: Injection-site reactions, GI (nausea, diarrhea), headache, rash, antibody development, positive ANA titer, cytopenia

iii. Etanercept (Enbrel)

- (a) Type of biologic: Fc portion of 100% humanized monoclonal antibody
- (b) Usually used in patients with JIA without systemic features
- (c) Dose: (1) 0.8 mg/kg (max 50 mg) subcutaneously once weekly or 0.4 mg/kg (max 25 mg) twice weekly (FDA label approved for children 2 years and older)
- (d) Onset of action within 2–4 weeks
- (e) Adverse effects: Injection-site reactions, GI (nausea, diarrhea), headache, rash, antibody development (non-neutralizing), positive ANA titer, cytopenia, inflammatory bowel disease

iv. Infliximab (Avsola, Inflectra, Renflexis, Remicade)

- (a) Type of biologic: Chimeric monoclonal antibody
- (b) Usually used in patients with JIA without systemic features
- (c) Dose: 5–10 mg/kg intravenously every 2–8 weeks. Higher doses of 10–20 mg/kg have been documented as safe (not FDA approved for JIA).
- (d) Onset of action within 2–4 weeks
- (e) Adverse effects: GI (nausea, diarrhea), headache, rash, infusion-related reactions (can pre-medicate with acetaminophen and diphenhydramine or, if severe reaction, steroids), antibody development (can be reduced by coadministration with methotrexate), positive ANA titer, cytopenia. Infliximab is contraindicated at doses higher than 5 mg/kg in patients with moderate or severe heart failure.

- v. Golimumab (Simponi Aria)
 - (a) 100% humanized monoclonal antibody
 - (b) Used for polyarticular JIA
 - (c) Dose (FDA approved for children 2 years and older):
 - (1) 80 mg/m²/dose intravenously at weeks 0 and 4 and then every 8 weeks thereafter
 - (2) Adverse effects: Antibody development, positive ANA titer, infections, cytopenia
- c. T-cell costimulation inhibitors – Abatacept (Orencia)
 - i. Mechanism of action: T-cell costimulation inhibitor
 - ii. Usually used for patients with polyarticular JIA
 - iii. Usually considered second-line therapy for patients with refractory disease whose therapy with TNF inhibitors has failed
 - iv. Intravenous dose: 10 mg/kg; repeat dose at 2 and 4 weeks after initial infusion and every 4 weeks thereafter (FDA label approved for patients 6 years and older)
 - v. Subcutaneous dose (FDA label approved for patients 2 years and older)
 - (a) 10–24 kg: 50 mg once weekly.
 - (b) 25–49 kg: 87.5 mg once weekly
 - (c) 50 kg or greater: 125 mg once weekly
 - vi. Onset of action: About 3 months
 - vii. Adverse effects: Headache, nausea, respiratory infections, antibody development
- d. IL-6 receptor antibody – Tocilizumab (Actemra)
 - i. Mechanism of action: Inhibits IL-6–mediated signaling by binding to both soluble and membrane-bound IL-6 receptors. Note: IL-6 is a proinflammatory cytokine produced by T cells and B cells.
 - ii. Usually considered second-line therapy for patients with refractory disease whose therapy with TNF inhibitors has failed
 - iii. FDA approved for patients 2 years and older with polyarticular or systemic JIA
 - iv. Polyarticular JIA dose
 - (a) Weight less than 30 kg: 10 mg/kg/dose intravenously every 4 weeks OR 162 mg/dose subcutaneously every 3 weeks
 - (b) Weight 30 kg or greater: 8 mg/kg intravenously every 4 weeks OR 162 mg/dose subcutaneously every 2 weeks
 - v. Systemic JIA dose
 - (a) Weight less than 30 kg: 12 mg/kg intravenously every 2 weeks OR 162 mg/dose subcutaneously every 2 weeks
 - (b) Weight 30 kg or greater: 8 mg/kg intravenously every 2 weeks OR 162 mg/dose subcutaneously every week
 - vi. Adverse effects: Thrombocytopenia, neutropenia, LFT abnormalities, lipid abnormalities, infusion reactions, injection-site reactions (subcutaneous formulation)
 - vii. Avoid initiating tocilizumab in patients with an absolute neutrophil count less than 2000 cells/mm³, Plt less than 100,000 cells/mm³, and AST/ALT 1.5 times the upper limit of normal.
- e. Janus kinase (JAK) inhibitors – Tofacitinib (Xeljanz)
 - i. Mechanism of action: Inhibition of JAK enzymes → prevents cytokine- or growth factor–mediated gene expression and intracellular activity of immune cells
 - ii. Usually considered second-line therapy for patients with refractory disease for whom TNF inhibitor therapy has failed
 - iii. FDA approved for patients 2 years and older weighing 10 kg or more with polyarticular JIA
 - iv. Dose
 - (a) Only biologic drug class that is available in an oral formulation

- (b) Oral solution and immediate-release tablets may be converted on a 1:1 basis. Extended-release tablets are only used in the adult population and are NOT bioequivalent to immediate-release tablets or oral solution.
 - (c) Weight 10–19 kg: Oral solution (1 mg/mL): 3.2 mg twice daily
 - (d) Weight 20–39 kg: Oral solution (1 mg/mL): 4 mg twice daily
 - (e) Weight 40 kg or higher: Oral solution (1 mg/mL) or immediate-release tablet: 5 mg twice daily
 - (f) Adverse effects: Infection, neutropenia, anemia
 - (g) Assess baseline CBC; do not initiate therapy in patients with an absolute lymphocyte count less than 500 cells/mm³, ANC less than 1000 cells/mm³, or hemoglobin less than 9 g/dL.
- f. Others
- i. Anakinra (Kineret) – IL-1 inhibitor
 - ii. Canakinumab (Ilaris) – Humanized anti-IL-1 antibody
 - iii. Rilonacept (Arcalyst) – IL-1 blocker (fusion protein that incorporates parts of the IL-1 receptor)
 - iv. Rituximab (Rituxan) – Anti-CD20 antibody
 - v. Tofacitinib (Xeljanz) – JAK inhibitor
 - vi. Secukinumab (Cosentyx) – Anti-IL-17 monoclonal antibody
6. Combination therapy: Nonbiologic DMARD plus biologic DMARD – The most common combination consists of methotrexate and a TNF inhibitor. Intra-articular steroids and NSAIDs are used as adjuncts.

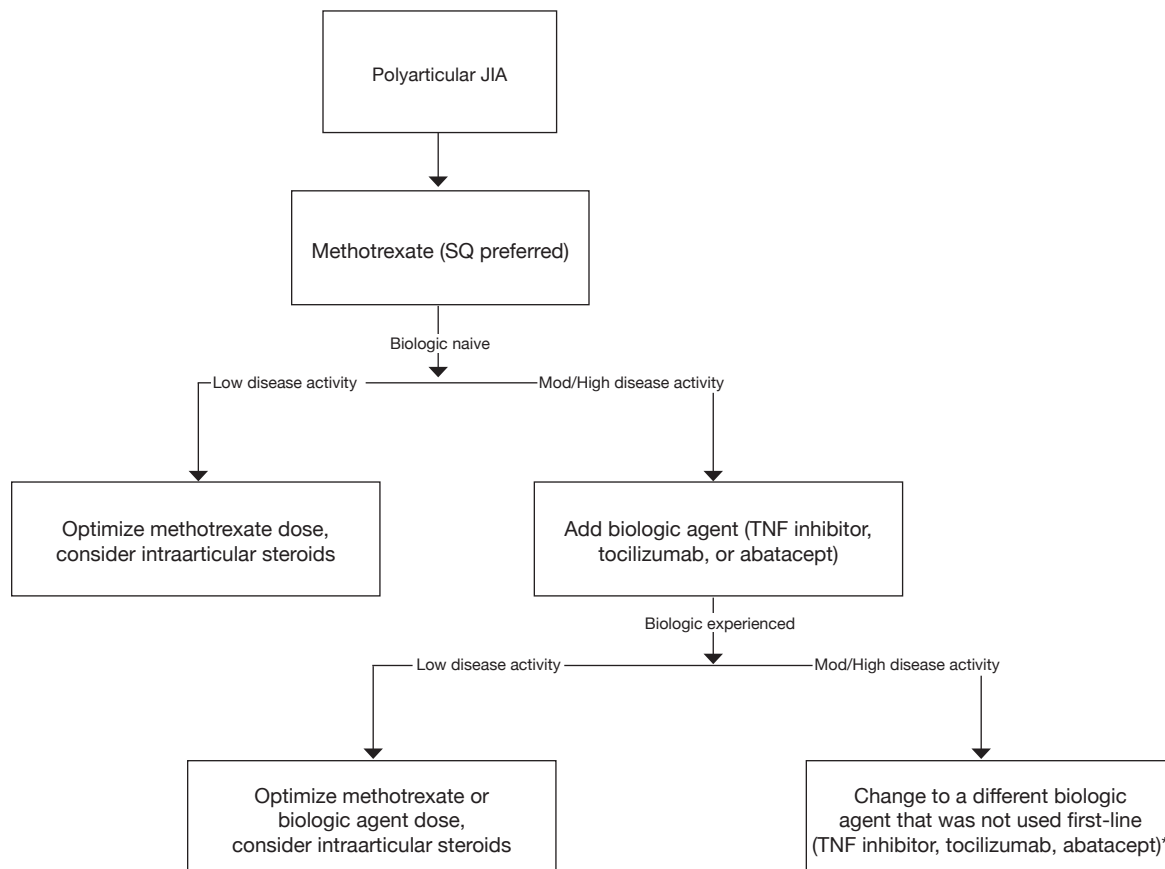


Figure 1. Treatment algorithm for children with polyarticular juvenile idiopathic arthritis.

*If initial therapy included a TNF inhibitor, it is preferred to change to tocilizumab or abatacept and then to a second TNF inhibitor.

JIA = juvenile idiopathic arthritis; SQ = subcutaneous(ly); TNF = tumor necrosis factor.

Table 3. General Treatment Guide for JIA

Drug Class	Commonly Used Drugs	Use in JIA
Systemic steroids	Prednisone Methylprednisolone	Systemic or polyarticular JIA
Intra-articular steroids	Triamcinolone acetonide Triamcinolone hexacetonide	Oligoarticular/polyarticular JIA; intra-articular injections can also be used in polyarticular JIA
NSAIDs	Naproxen Ibuprofen Meloxicam Indomethacin	Systemic, polyarticular, or enthesitis-related JIA
Nonbiologic DMARDs	Methotrexate	Systemic, polyarticular, or enthesitis-related JIA
	Leflunomide	Systemic or polyarticular JIA
	Sulfasalazine	Enthesitis-related JIA
TNF inhibitors	Adalimumab Infliximab Etanercept Golimumab	Polyarticular, oligoarticular, or enthesitis-related JIA
T-cell costimulation inhibitors	Abatacept	Polyarticular and oligoarticular JIA
IL-1 inhibitors	Anakinra Canakinumab Rilonacept	Systemic JIA
IL-6 inhibitors	Tocilizumab	Systemic or polyarticular JIA
Anti-CD20 antibody	Rituximab	Polyarticular JIA
JAK inhibitors	Tofacitinib	Polyarticular, psoriatic, enthesitis-related JIA

DMARD = disease-modifying antirheumatic drug; JAK = Janus kinase; JIA = juvenile idiopathic arthritis; TNF = tumor necrosis factor.

Patient Cases

- A 17-year-old female adolescent is being followed by pediatric rheumatology for JIA diagnosed 10 years ago. The patient currently takes methotrexate 25 mg subcutaneously every Friday, folic acid 1 mg orally once daily, naproxen 250 mg orally twice daily, and etanercept 25 mg subcutaneously twice weekly. Her physical examination is notable for right wrist swelling and decreased range of motion in flexion and extension. The patient describes pain with range of motion. Which therapy is most appropriate to recommend?

 - Initiate prednisone 60 mg orally once daily.
 - Increase methotrexate to 30 mg subcutaneously every Friday.
 - Initiate anakinra 100 mg subcutaneously once daily.
 - Administer triamcinolone hexacetonide in the affected joint.

Patient Cases (*continued*)

4. A 9-year-old girl (weight 30 kg) is followed by pediatric rheumatology for polyarticular JIA. The patient's prescribed regimen consists of adalimumab 40 mg subcutaneously every other week, methotrexate 15 mg orally once weekly, folic acid 1 mg orally once daily, and naproxen 250 mg orally twice daily. The patient's father states that the patient has been nonadherent to methotrexate because of nausea and that she completely stopped taking it about 6 weeks ago. She did well initially, but her symptoms began to worsen last week, and she is in pain. Her physical examination is notable for swelling in the bilateral elbows, wrists, knees, and ankles. She also has pain and a limited range of motion in these joints. Which recommendation is most appropriate for this patient?
- A. Reinitiate methotrexate 15 mg orally once weekly.
 - B. Initiate methotrexate 15 mg subcutaneously once weekly.
 - C. Increase the adalimumab dose to 40 mg subcutaneously every week.
 - D. Initiate prednisone 30 mg orally daily and methotrexate 15 mg subcutaneously once weekly.

III. SEVERE COMBINED IMMUNODEFICIENCY

- A. Definition: Heterogeneous group of disorders arising from a disturbance in the development and function of both T cells and B cells
- B. Epidemiology: 1 in 40,000–50,000 live births
- C. Classification and Pathogenesis
 - 1. T-cell negative, B-cell positive, natural killer cell–negative (T-B+NK-) SCID
 - a. X-linked SCID (about 50% of all cases, most common type): Defects in the IL-2 receptor gene (*IL2RG*) on the X chromosome encoding the cytokine receptor subunit γ_c ; this subunit is shared by many cytokine receptors and is important for lymphocyte development and function, affects only males
 - b. Janus-associated kinase 3 (JAK3) (about 6% of all cases): Defect in the JAK3 gene that encodes for the JAK3 enzyme within lymphocytes, which is necessary for the proper function of the γ_c subunit; this leads to the failure of several cytokine signaling pathways and results in impaired lymphocyte development/function
 - 2. T-B+NK+ SCID (about 10% of all cases): Usually a defect in the IL-7 receptor- α chain, which is important for cytokine signaling and T-cell development
 - 3. T-B-NK+ SCID (20%–30% of all cases): Defects in V(D)J recombination that randomly combines variable, diverse, and joining gene segments in lymphocytes to generate a diverse repertoire of T- and B-cell receptors that can recognize potential pathogens. Defects in several of these pathways are associated with radiation/chemotherapy sensitivity because some of the proteins encoded by these genes are also involved in DNA repair.
 - 4. T-B-NK-SCID (about 15% of all cases): Adenosine deaminase (ADA) deficiency caused by mutation of the *ADA* gene is the most common type – Accumulation of adenosine and deoxyadenosine within cells – Apoptosis of thymocytes and lymphocytes

*Note: Even though some types have B cells present, the function of B cells is significantly impaired.

D. Clinical Manifestations

1. Opportunistic/recurrent infections (e.g., thrush, *Pneumocystis jiroveci* pneumonia [PJP], CMV, parainfluenza, herpesviruses)
2. Recurrent fevers
3. Diarrhea
4. Failure to thrive
5. Adverse reactions to live vaccines

E. Diagnosis

1. Lymphopenia (absolute lymphocyte count less than 2500 cells/mm³), absent antibody formation, low-to-absent immunoglobulin concentration, maternal T cells in the circulation
2. Absence of thymic shadow on chest radiography
3. Newborn screening has facilitated early diagnosis – Has been implemented in all states

F. Treatment

1. Hematopoietic cell transplantation (HCT) – Critical for survival. SCID is usually fatal within the first year of life if left untreated. Younger age at time of HCT (younger than 3½ months) and matched sibling donor type are associated with better survival. Active infection at time of transplantation is associated with worse outcomes.
2. Isolation precautions (before HCT)
3. Vaccinations
 - a. Before HCT
 - i. Live vaccines are contraindicated.
 - ii. Household contacts should avoid receiving live attenuated influenza vaccine (LAIV).
 - b. After HCT
 - i. Usually need to wait at least 6 months to receive inactivated vaccines
 - ii. MMR and varicella can be given if the patient is seronegative for measles (or varicella); the timing is 24 months or more after HCT; no graft-vs.-host disease present, and patient is not receiving immunosuppressive medication
 - iii. Neither LAIV, zoster, nor rotavirus is recommended.
4. Blood products must be irradiated to prevent transfusion-related graft-vs.-host disease and must be CMV negative to prevent viral transmission.
5. Breastfeeding discouraged if the mother is positive for CMV antibodies
6. Gene therapy
 - a. Usually done through either gene addition (using certain viruses to integrate into the human genome) or gene editing (currently investigational)
 - b. Early gene therapy using certain retroviruses was associated with insertional mutagenesis causing leukemia. Newer gene therapy approaches have further modified the viral vectors and appear to be safer.
7. Immunoglobulin (e.g., Gammagard, Gamunex-C, Octagam) therapy should be initiated as soon as possible to prevent infections before HCT, and replacement is sometimes continued after HCT until immune reconstitution is sufficient. Dose: 400–600 mg/kg every 3–4 weeks. Target IgG concentrations in hypogammaglobulinemia are greater than 500–800 mg/dL.
 - a. Helps prevent infections and hospital admissions and improves quality of life
 - b. Adverse effects: Rate-related reactions such as chills, headache, dyspnea, and urticaria, which can be managed with acetaminophen, diphenhydramine, steroids; “flu-like” symptoms during acute infection (thought to be caused by lysis of bacteria and cytokine release), aseptic meningitis

- c. Vaccination after receipt of immunoglobulin replacement
 - i. Response to vaccines may be diminished.
 - ii. Lack of robust data regarding whether patients with primary immunodeficiencies and receiving immunoglobulin therapy should receive routine inactivated vaccines: The 2013 IDSA (Infectious Diseases Society of America) guidelines do not recommend inactivated vaccines (except for the inactivated influenza vaccine [IIV])
- 8. Antimicrobial prophylaxis
 - a. Often broad-spectrum coverage, including PJP antifungal and antiviral prophylaxis
 - b. Respiratory syncytial virus (RSV) prophylaxis with palivizumab administered during RSV season

Patient Case

5. Which vaccine is most likely to be unsafe to administer to a 6-month-old infant with a medical history of SCID who is awaiting HCT and receiving intravenous immunoglobulin replacement therapy?
- A. Influenza (inactivated).
 - B. Diphtheria, tetanus, acellular pertussis (DTaP).
 - C. Pneumococcal conjugate vaccine.
 - D. Rotavirus.

IV. VACCINATIONS

- A. 2021 CDC Vaccination Schedule (Figure 2)
- B. Vaccine Excipient Summary is available at <https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/b/excipient-table-2.pdf> (last updated November 2021).
- C. Standard Childhood Immunizations (Table 4)
 - 1. Diphtheria, tetanus, acellular pertussis (DTaP) (Daptacel or Infanrix)
 - a. DTaP (Daptacel, Infanrix): Five doses (2, 4, 6, 15–18 months, 4–6 years)
 - b. Tetanus, diphtheria, acellular pertussis (Tdap) (Adacel, Boostrix): One dose (11–12 years)
 - c. DTaP versus Tdap:
 - i. Tdap has lower concentrations of diphtheria toxoid than DTaP.
 - ii. Tdap is used as a booster for children older than 10 years or as part of a catch-up series for children older than 7 years.
 - d. DT (diphtheria tetanus) without pertussis is available for patients with a contraindication or precaution to pertussis. Contraindications to the pertussis component include progressive or poorly controlled neurologic disorder. Caution is advised in children with a history of seizures or conditions that predispose to seizures. Similarly, Td without pertussis is used as a booster for children older than 7 years who should not receive the pertussis component.
 - e. Adverse effects: Injection-site reaction, limb swelling, persistent/inconsolable crying (more than 3 hours), hypotonic-hyporesponsive episode, febrile seizures, fever

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger

UNITED STATES
2022

Vaccines in the Child and Adolescent Immunization Schedule*

Vaccine	Abbreviation(s)	Trade name(s)
Dengue vaccine	DENVACYD	Dengvaxia ^a
Diphtheria, tetanus, and acellular pertussis vaccine	DTaP	Daptacel ^a Infanrix ^a
Diphtheria, tetanus vaccine	DT	No trade name
<i>Haemophilus influenzae</i> type b vaccine	Hib (PRP-T)	ActHib ^a Hibertix ^a
	Hib (PRP-OMP)	PedvaxHib ^a
Hepatitis A vaccine	HepA	Havrix ^a Vaqta ^a
Hepatitis B vaccine	HepB	Engerix-B ^a Recombivax HB ^a
Human papillomavirus vaccine	HPV	Gardasil 9 ^a
Influenza vaccine (inactivated)	IV4	Multiple
Influenza vaccine (live, attenuated)	LAIV4	FluMist ^a Quadrivalent
Measles, mumps, and rubella vaccine	MMR	M-M-R II ^a
Meningococcal serogroups A, C, W, Y vaccine	MenACWY-D	Menactra ^a
	MenACWY-CRM	Menveo ^a
	MenACWY-TT	MenQuadfi ^a
Meningococcal serogroup B vaccine	MenB-4C	Bexsero ^a
	MenB-FHbp	Trumenba ^a
Pneumococcal 13-valent conjugate vaccine	PCV13	Prevnar 13 ^a
Pneumococcal 23-valent polysaccharide vaccine	PPSV23	Pneumovax 23 ^a
Poliovirus vaccine (inactivated)	IPV	IPOL ^a
Rotavirus vaccine	RV1 RV5	Rotarix ^a RotaTeq ^a
Tetanus, diphtheria, and acellular pertussis vaccine	Tdap	Adacel ^a Boostrix ^a
Tetanus and diphtheria vaccine	Td	Tenivac ^a Tdva ^a
Varicella vaccine	VAR	Varivax ^a
Combination vaccines (use combination vaccines instead of separate injections when appropriate)		
DTaP, hepatitis B, and inactivated poliovirus vaccine	DTaP-HepB-IPV	Pediarix ^a
DTaP, inactivated poliovirus, and <i>Haemophilus influenzae</i> type b vaccine	DTaP-IPV/Hib	Pentacel ^a
DTaP and inactivated poliovirus vaccine	DTaP-IPV	Kinrix ^a Quadracel ^a
DTaP, inactivated poliovirus, <i>Haemophilus influenzae</i> type b, and hepatitis B vaccine	DTaP-IPV-Hib-HepB	Vaxelis ^a
Measles, mumps, rubella, and varicella vaccine	MMRV	ProQuad ^a

*Administer recommended vaccines if immunization history is incomplete or unknown. Do not restart or add doses to vaccine series for extended intervals between doses. When a vaccine is not administered at the recommended age, administer at a subsequent visit. The use of trade names is for identification purposes only and does not imply endorsement by the ACP or CDC.

How to use the child and adolescent immunization schedule

- 1 Determine recommended vaccine by age (Table 1)
- 2 Determine recommended interval for catch-up vaccination (Table 2)
- 3 Assess need for additional recommended vaccines by medical condition or other indication (Table 3)
- 4 Review vaccine types, frequencies, intervals, and considerations for special situations (Notes)
- 5 Review contraindications and precautions for vaccine types (Appendix)

Recommended by the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/acip) and approved by the Centers for Disease Control and Prevention (www.cdc.gov), American Academy of Pediatrics (www.aap.org), American Academy of Family Physicians (www.aafp.org), American College of Obstetricians and Gynecologists (www.acog.org), American College of Nurse-Midwives (www.midwife.org), American Academy of Physician Assistants (www.aapa.org), and National Association of Pediatric Nurse Practitioners (www.napnap.org).

Report

- Suspected cases of reportable vaccine-preventable diseases or outbreaks to your state or local health department
- Clinically significant adverse events to the Vaccine Adverse Event Reporting System (VAERS) at www.vaers.hhs.gov or 800-822-7967

Questions or comments

Contact www.cdc.gov/cdc-info or 800-CDC-INFO (800-232-4636), in English or Spanish, 8 a.m.–8 p.m. ET, Monday through Friday, excluding holidays



Download the CDC Vaccine Schedules app for providers at www.cdc.gov/vaccines/schedules/hcp/schedule-app.html

Helpful information

- Complete Advisory Committee on Immunization Practices (ACIP) recommendations: www.cdc.gov/vaccines/hcp/acip-recs/index.html
- General Best Practice Guidelines for Immunization (including contraindications and precautions): www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html
- Vaccine information statements: www.cdc.gov/vaccines/hcp/vis/index.html
- Manual for the Surveillance of Vaccine-Preventable Diseases (including case identification and outbreak response): www.cdc.gov/vaccines/pubs/surv-manual
- ACIP Shared Clinical Decision-Making Recommendations www.cdc.gov/vaccines/acip-scdm-aqis.html

Scan QR code for access to online schedule



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U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Figure 2. CDC recommended child and adolescent immunization schedule for ages 18 years or younger, United States 2022. Available at www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-combined-schedule-bw.pdf.

Table 1 Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

These recommendations must be read with the notes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the green bars. To determine minimum intervals between doses, see the catch-up schedule (Table 2).

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos	18 mos	19–23 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
Hepatitis B (HepB)	1 st dose	← 2 nd dose →					3 rd dose										
Rotavirus (RV): RV1 (2-dose series), RV5 (3-dose series)		1 st dose	2 nd dose	See Notes													
Diphtheria, tetanus, acellular pertussis (DTaP <7 yrs)		1 st dose	2 nd dose	2 nd dose	3 rd dose			4 th dose				5 th dose					
<i>Haemophilus influenzae</i> type b (Hib)		1 st dose	2 nd dose	2 nd dose	See Notes		3 rd or 4 th dose	See Notes									
Pneumococcal conjugate (PCV13)		1 st dose	2 nd dose	2 nd dose	3 rd dose		4 th dose										
Inactivated poliovirus (IPV <18 yrs)		1 st dose	2 nd dose	3 rd dose								4 th dose					
Influenza (IIV4)																	
Influenza (LAIV4)																	
Measles, mumps, rubella (MMR)					See Notes		1 st dose					2 nd dose					
Varicella (VAR)							1 st dose					2 nd dose					
Hepatitis A (HepA)					See Notes												
Tetanus, diphtheria, acellular pertussis (Tdap ≥7 yrs)														1 dose			
Human papillomavirus (HPV)														See Notes			
Meningococcal (MenACWY-D ≥9 mos, MenACWY-CRM ≥2 mos, MenACWY-TT ≥2 years)														1 st dose		2 nd dose	
Meningococcal B (MenB-4C, MenB-FHbp)																	
Pneumococcal polysaccharide (PPSV23)																	
Dengue (DENVACYD, 9–16 yrs)																	

Figure 2. (continued)

Table 2**Recommended Catch-up Immunization Schedule for Children and Adolescents Who Start Late or Who Are More than 1 Month Behind, United States, 2022**

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. **Always use this table in conjunction with Table 1 and the Notes that follow.**

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B	Birth	4 weeks	8 weeks and at least 16 weeks after first dose minimum age for the final dose is 24 weeks		
Rotavirus	6 weeks Maximum age for first dose is 14 weeks, 6 days. 6 weeks	4 weeks	4 weeks maximum age for final dose is 8 months, 0 days		
Diphtheria, tetanus, and acellular pertussis	6 weeks	4 weeks	4 weeks	6 months	6 months
<i>Haemophilus influenzae</i> type b	6 weeks	No further doses needed if first dose was administered at age 15 months or older. 4 weeks if first dose was administered before the 1 st birthday. 8 weeks (as final dose) if first dose was administered at age 12 through 14 months.	No further doses needed if previous dose was administered at age 15 months or older 4 weeks if current age is younger than 12 months and first dose was administered at younger than age 7 months and at least 1 previous dose was PIP-T (ActHib [®] , Pentacel [®] , Hibex [®] , Vaxelis [®] or unknown 8 weeks and age 12 through 59 months (as final dose) if current age is younger than 12 months and first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months and first dose was administered before the 1 st birthday and second dose was administered at younger than 15 months; OR if both doses were PedvaxHib [®] and were administered before the 1 st birthday	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1 st birthday.	
Pneumococcal conjugate	6 weeks	No further doses needed for healthy children if first dose was administered at age 24 months or older 4 weeks if first dose was administered before the 1 st birthday 8 weeks (as final dose for healthy children) if previous dose was administered at the 1 st birthday or after	No further doses needed for healthy children if previous dose was administered at age 24 months or older 4 weeks if current age is younger than 12 months and previous dose was administered at <7 months old 8 weeks (as final dose for healthy children) if previous dose was administered between 7–11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was administered before age 12 months	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	4 weeks	4 weeks if current age is <4 years 6 months (as final dose) if current age is 4 years or older	6 months (minimum age 4 years for final dose)	
Measles, mumps, rubella	12 months	4 weeks			
Varicella	12 months	3 months			
Hepatitis A	12 months	6 months			
Meningococcal ACWY	2 months MenACWY-CRM 9 months MenACWY-D 2 years MenACWY-TT	8 weeks	See Notes	See Notes	
Children and adolescents age 7 through 18 years					
Meningococcal ACWY	Not applicable (N/A)	8 weeks			
Tetanus, diphtheria, tetanus, diphtheria, and acellular pertussis	7 years	4 weeks	4 weeks if first dose of DTaP/DT was administered before the 1 st birthday 6 months (as final dose) if first dose of DTaP/DT or Tdap/Td was administered at or after the 1 st birthday	6 months if first dose of DTaP/DT was administered before the 1 st birthday	
Human papillomavirus	9 years	Routine dosing intervals are recommended.			
Hepatitis A	N/A	6 months			
Hepatitis B	N/A	4 weeks	8 weeks and at least 16 weeks after first dose		
Inactivated poliovirus	N/A	4 weeks	6 months A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.	
Measles, mumps, rubella	N/A	4 weeks			
Varicella	N/A	3 months if younger than age 13 years. 4 weeks if age 13 years or older			
Dengue	9 years	6 months	6 months		

Figure 2. (continued)

Table 3 Recommended Child and Adolescent Immunization Schedule by Medical Indication, United States, 2022

Always use this table in conjunction with Table 1 and the Notes that follow.

VACCINE	Pregnancy	Immunocompromised status (excluding HIV infection)	HIV infection CD4+ count ¹		Kidney failure, end-stage renal disease, or on hemodialysis	Heart disease or chronic lung disease	CSF leak or cochlear implant	Asplenia or persistent complement deficiencies	Chronic liver disease	Diabetes
			<15% or total CD4 cell count of <200/mm ³	≥15% and total CD4 cell count of ≥200/mm ³						
Hepatitis B										
Rotavirus		SCID ²								
Diphtheria, tetanus, and acellular pertussis (DTaP)										
<i>Haemophilus influenzae</i> type b										
Pneumococcal conjugate										
Inactivated poliovirus										
Influenza (IV4)										
Influenza (LAIV4)						Asthma, wheezing; 2–4 yrs ³				
Measles, mumps, rubella	*									
Varicella	*									
Hepatitis A										
Tetanus, diphtheria, and acellular pertussis (Tdap)										
Human papillomavirus	*									
Meningococcal ACWY										
Meningococcal B										
Pneumococcal polysaccharide										
Dengue										

Vaccination according to the routine schedule recommended
 Recommended for persons with an additional risk factor for which the vaccine would be indicated
 Vaccination is recommended, and additional doses may be necessary based on medical condition or vaccine. See Notes.
 Precaution—vaccine might be indicated if benefit of protection outweighs risk of adverse reaction
 Contraindicated or not recommended—vaccine should not be administered
 No recommendation/not applicable
 *Vaccinate after pregnancy

1 For additional information regarding HIV laboratory parameters and use of live vaccines, see the *General Best Practice Guidelines for Immunization*, "Altered Immunocompetence," at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html and Table 4-1 (footnote J) at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/contraindications.html.

2 Severe Combined Immunodeficiency

3 LAIV4 contraindicated for children 2–4 years of age with asthma or wheezing during the preceding 12 months

Figure 2. (continued)

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

For vaccination recommendations for persons ages 19 years or older, see the Recommended Adult Immunization Schedule, 2022.

Additional information

COVID-19 Vaccination

COVID-19 vaccines are recommended for use within the scope of the Emergency Use Authorization or Biologics License Application for the particular vaccine. ACIP recommendations for the use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html.

CDC's interim clinical considerations for use of COVID-19 vaccines can be found at www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html.

- Consult relevant ACIP statements for detailed recommendations at www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For calculating intervals between doses, 4 weeks = 28 days. Intervals of ≥4 months are determined by calendar months.
- Within a number range (e.g., 12–18), a dash (–) should be read as "through."
- Vaccine doses administered ≤4 days before the minimum age or interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum age or minimum interval should not be counted as valid and should be repeated as age appropriate. **The repeat dose should be spaced after the invalid dose by the recommended minimum interval.** For further details, see Table 3-1. Recommended and minimum ages and intervals between vaccine doses, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html.
- Information on travel vaccination requirements and recommendations is available at www.cdc.gov/travel/.
- For vaccination of persons with immunodeficiencies, see Table 8-1. Vaccination of persons with primary and secondary immunodeficiencies, in *General Best Practice Guidelines for Immunization* at www.cdc.gov/vaccines/hcp/acip-recs/general-recs/immunocompetence.html, and *Immunization in Special Clinical Circumstances* (In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. *Red Book: 2018 Report of the Committee on Infectious Diseases*. 31st ed. Itasca, IL: American Academy of Pediatrics; 2018:67–111).
- For information about vaccination in the setting of a vaccine-preventable disease outbreak, contact your state or local health department.
- The National Vaccine Injury Compensation Program (VICP) is a no-fault alternative to the traditional legal system for resolving vaccine injury claims. All routine child and adolescent vaccines are covered by VICP except for pneumococcal polysaccharide vaccine (PPSV23). For more information, see www.hrsa.gov/vaccinecompensation/index.html.

Dengue vaccination

(minimum age: 9 years)

Routine vaccination

- Age 9–16 years living in dengue endemic areas AND have laboratory confirmation of previous dengue infection
 - 3-dose series administered at 0, 6, and 12 months
- Endemic areas include Puerto Rico, American Samoa, US Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau. For updated guidance on dengue endemic areas and pre-vaccination laboratory testing see www.cdc.gov/mmwr/volumes/70/rr/r7006a1.html's [cid=r7006a1](http://www.cdc.gov/mmwr/volumes/70/rr/r7006a1.html#cid=r7006a1) and www.cdc.gov/dengue/vaccine/hcp/index.html

Diphtheria, tetanus, and pertussis (DTaP) vaccination (minimum age: 6 weeks [4 years for Kinrix® or Quadracel®])

Routine vaccination

- 5-dose series at age 2, 4, 6, 15–18 months, 4–6 years
 - Prospectively:** Dose 4 may be administered as early as age 12 months if at least 6 months have elapsed since dose 3.
 - Retrospectively:** A 4th dose that was inadvertently administered as early as age 12 months may be counted if at least 4 months have elapsed since dose 3.
- Catch-up vaccination**
 - Dose 5 is not necessary if dose 4 was administered at age 4 years or older and at least 6 months after dose 3.
 - For other catch-up guidance, see Table 2.

Special situations

- Wound management in children less than age 7 years with history of 3 or more doses of tetanus-toxoid-containing vaccine: For all wounds except clean and minor wounds, administer DTaP if more than 5 years since last dose of tetanus-toxoid-containing vaccine. For detailed information, see www.cdc.gov/mmwr/volumes/67/rr/r6702a1.htm.

Haemophilus influenzae type b vaccination

(minimum age: 6 weeks)

Routine vaccination

- ActHib®, Hibertix®, Pentacel®, or Vaxelis®**, 4-dose series (3 dose primary series at age 2, 4, and 6 months, followed by a booster dose* at age 12–15 months)
 - *Vaxelis® is not recommended for use as a booster dose. A different Hib-containing vaccine should be used for the booster dose.
- PedvaxHIB®**: 3-dose series (2-dose primary series at age 2 and 4 months, followed by a booster dose at age 12–15 months)
- Catch-up vaccination**
 - Dose 1 at age 7–11 months:** Administer dose 2 at least 4 weeks later and dose 3 (final dose) at age 12–15 months or 8 weeks after dose 2 (whichever is later).
 - Dose 1 at age 12–14 months:** Administer dose 2 (final dose) at least 8 weeks after dose 1.

- Dose 1 before age 12 months and dose 2 before age 15 months:** Administer dose 3 (final dose) at least 8 weeks after dose 2.
- 2 doses of PedvaxHIB® before age 12 months:** Administer dose 3 (final dose) at 12–59 months and at least 8 weeks after dose 2.
- 1 dose administered at age 15 months or older:** No further doses needed
- Unvaccinated at age 15–59 months:** Administer 1 dose.
- Previously unvaccinated children age 60 months or older who are not considered high risk:** Do not require catch-up vaccination. For other catch-up guidance, see Table 2. Vaxelis® can be used for catch-up vaccination in children less than age 5 years. Follow the catch-up schedule even if Vaxelis® is used for one or more doses. For detailed information on use of Vaxelis®, see www.cdc.gov/mmwr/volumes/69/wr/mm6905a5.htm.

Special situations

Chemotherapy or radiation treatment:

- Age 12–59 months**
 - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
 - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose
- Doses administered within 14 days of starting therapy or during therapy should be repeated at least 3 months after therapy completion.**

Hematopoietic stem cell transplant (HSCT):

- 3-dose series 4 weeks apart starting 6 to 12 months after successful transplant, regardless of Hib vaccination history

Anatomic or functional asplenia (including sickle cell disease):

- Age 12–59 months**
 - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
 - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose
- Unvaccinated* persons age 5 years or older**
 - 1 dose

Elective splenectomy:

- Unvaccinated* persons age 15 months or older
 - 1 dose (preferably at least 14 days before procedure)

HIV infection:

- Age 12–59 months**
 - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
 - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose
- Unvaccinated* persons age 5–18 years**
 - 1 dose

Immunoglobulin deficiency, early component complement deficiency:

- Age 12–59 months**
 - Unvaccinated or only 1 dose before age 12 months: 2 doses, 8 weeks apart
 - 2 or more doses before age 12 months: 1 dose at least 8 weeks after previous dose
- *Unvaccinated =** Less than routine series (through age 14 months) OR no doses (age 15 months or older)

Figure 2. (continued)

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

Hepatitis A vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series (minimum interval: 6 months) at age 12–23 months

Catch-up vaccination

- Unvaccinated persons through age 18 years should complete a 2-dose series (minimum interval: 6 months).
- Persons who previously received 1 dose at age 12 months or older should receive dose 2 at least 6 months after dose 1.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix**[®], as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).

International travel

- Persons traveling to or working in countries with high or intermediate endemic hepatitis A (www.cdc.gov/travel/):
- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2 doses, separated by at least 6 months, between age 12–23 months.
- **Unvaccinated age 12 months or older:** Administer dose 1 as soon as travel is considered.

Hepatitis B vaccination (minimum age: birth)

Birth dose (monovalent HepB vaccine only)

- **Mother is HBsAg-negative:**
 - All medically stable infants ≥2,000 grams: 1 dose within 24 hours of birth
 - Infants <2,000 grams: Administer 1 dose at chronological age 1 month or hospital discharge (whichever is earlier and even if weight is still <2,000 grams).

Mother is HBsAg-positive:

- Administer **HepB vaccine** and **hepatitis B immune globulin (HBIG)** (in separate limbs) within 12 hours of birth, regardless of birth weight. For infants <2,000 grams, administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
- Test for HBsAg and anti-HBs at age 9–12 months. If HepB series is delayed, test 1–2 months after final dose.

Mother's HBsAg status is unknown:

- Administer **HepB vaccine** within 12 hours of birth, regardless of birth weight.
- For infants <2,000 grams, administer **HBIG** in addition to HepB vaccine (in separate limbs) within 12 hours of birth. Administer 3 additional doses of vaccine (total of 4 doses) beginning at age 1 month.
- Determine mother's HBsAg status as soon as possible. If mother is HBsAg-positive, administer **HBIG** to infants ≥2,000 grams as soon as possible, but no later than 7 days of age.

Routine series

- 3-dose series at age 0, 1–2, 6–18 months (use monovalent HepB vaccine for doses administered before age 6 weeks)
- Infants who did not receive a birth dose should begin the series as soon as feasible (see Table 2).

Figure 2. (continued)

- Administration of 4 doses is permitted when a combination vaccine containing HepB is used after the birth dose.

- **Minimum age for the final (3rd or 4th) dose:** 24 weeks 8 weeks / dose 1 to dose 2; 4 weeks / dose 2 to dose 3; 16 weeks / dose 3 to dose 4 (when 4 doses are administered, substitute dose 4 for dose 3 in these calculations)

Catch-up vaccination

- Unvaccinated persons should complete a 3-dose series at 0, 1–2, 6 months.
- Adolescents age 11–15 years may use an alternative 2-dose schedule with at least 4 months between doses (adult formulation **Recombivax HB**[®] only).
- Adolescents age 18 years or older may receive a 2-dose series of HepB (**HepSav-B**) at least 4 weeks apart.
- Adolescents age 18 years or older may receive the combined HepA and HepB vaccine, **Twinrix**[®], as a 3-dose series (0, 1, and 6 months) or 4-dose series (3 doses at 0, 7, and 21–30 days, followed by a booster dose at 12 months).
- For other catch-up guidance, see Table 2.

Special situations

- Revaccination is not generally recommended for persons with a normal immune status who were vaccinated as infants, children, adolescents, or adults.
- **Post-vaccination serology testing and revaccination** (if anti-HBs < 10 mIU/mL) is recommended for certain populations, including:
 - Infants born to HBsAg-positive mothers
 - Hemodialysis patients
 - Other immunocompromised persons
- For detailed revaccination recommendations, see www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/hepb.html.

Human papillomavirus vaccination (minimum age: 9 years)

Routine and catch-up vaccination

- HPV vaccination routinely recommended at **age 11–12 years (can start at age 9 years)** and catch-up HPV vaccination recommended for all persons through age 18 years if not adequately vaccinated:
 - 2- or 3-dose series depending on age at initial vaccination:
 - **Age 9–14 years at initial vaccination:** 2-dose series at 0, 6–12 months (minimum interval: 5 months; repeat dose if administered too soon)
 - **Age 15 years or older at initial vaccination:** 3-dose series at 0, 1–2 months, 6 months (minimum intervals: dose 1 to dose 2: 4 weeks / dose 2 to dose 3: 12 weeks / dose 1 to dose 3: 5 months; repeat dose if administered too soon)
- **Interrupted schedules:** If vaccination schedule is interrupted, the series does not need to be restarted.
- No additional dose recommended when any HPV vaccine series has been completed using the recommended dosing intervals.

Special situations

- **Immunocompromising conditions, including HIV infection:** 3-dose series, even for those who initiate vaccination at age 9 through 14 years.
- **History of sexual abuse or assault:** Start at age 9 years.

- **Pregnancy:** Pregnancy testing not needed before vaccination; HPV vaccination not recommended until after pregnancy; no intervention needed if vaccinated while pregnant

Influenza vaccination

(minimum age: 6 months [IV], 2 years [LANV], 18 years [recombinant influenza vaccine, RIV4])

Routine vaccination

- Use any influenza vaccine appropriate for age and health status annually:
 - 2 doses, separated by at least 4 weeks, for **children age 6 months–8 years** who have received fewer than 2 influenza vaccine doses before July 1, 2021, or whose influenza vaccination history is unknown (administer dose 2 even if the child turns 9 between receipt of dose 1 and dose 2)
 - 1 dose for **children age 6 months–8 years** who have received at least 2 influenza vaccine doses before July 1, 2021
 - 1 dose for **all persons age 9 years or older**
- For the 2021–2022 season, see www.cdc.gov/mmwr/volumes/70/rr/r7005a1.htm.
- For the 2022–23 season, see the 2022–23 ACIP Influenza vaccine recommendations.

Special situations

- **Egg allergy, hives only:** Any influenza vaccine appropriate for age and health status annually
- **Egg allergy with symptoms other than hives** (e.g., angioedema, respiratory distress) or required epinephrine or another emergency medical intervention: see Appendix listing contraindications and precautions
- **Severe allergic reaction (e.g., anaphylaxis) to a vaccine component or a previous dose of any influenza vaccine:** see Appendix listing contraindications and precautions

Measles, mumps, and rubella vaccination (minimum age: 12 months for routine vaccination)

Routine vaccination

- 2-dose series at age 12–15 months, age 4–6 years
- MMR or MMRV may be administered
- Note:** For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.

Catch-up vaccination

- Unvaccinated children and adolescents: 2-dose series at least 4 weeks apart
- The maximum age for use of MMRV is 12 years.
- Minimum interval between MMRV doses: 3 months

Special situations

International travel

- **Infants age 6–11 months:** 1 dose before departure; revaccinate with 2-dose series at age 12–15 months (12 months for children in high-risk areas) and dose 2 as early as 4 weeks later.
- **Unvaccinated children age 12 months or older:** 2-dose series at least 4 weeks apart before departure

Notes

Recommended Child and Adolescent Immunization Schedule for ages 18 years or younger, United States, 2022

Chronic liver disease, alcoholism:

- Age ≥ 18 years
- No history of PPSV23: 1 dose PPSV23 (at least 8 weeks after any prior PCV13 dose)

**Incomplete series* = Not having received all doses in either the recommended series or an age-appropriate catch-up series. See Tables 8, 9, and 11 in the ACIP pneumococcal vaccine recommendations (www.cdc.gov/mmwr/pdf/rr/r15911.pdf) for complete schedule details.

Poliovirus vaccination

(minimum age: 6 weeks)

Routine vaccination

- 4-dose series at ages 2, 4, 6–18 months, 4–6 years; administer the final dose on or after age 4 years and at least 6 months after the previous dose.
- 4 or more doses of IPV can be administered before age 4 years when a combination vaccine containing IPV is used. However, a dose is still recommended on or after age 4 years and at least 6 months after the previous dose.

Catch-up vaccination

- In the first 6 months of life, use minimum ages and intervals only for travel to a polio-endemic region or during an outbreak.
- IPV is not routinely recommended for U.S. residents age 18 years or older.

Series containing oral polio vaccine (OPV), either mixed OPV-IPV or OPV-only series:

- Total number of doses needed to complete the series is the same as that recommended for the U.S. IPV schedule. See www.cdc.gov/mmwr/volumes/66/wr/mm6601a6.htm?_r=0&cid=mm6601a6_w.
- Only trivalent OPV (tOPV) counts toward the U.S. vaccination requirements.

- Doses of OPV administered before April 1, 2016, should be counted (unless specifically noted as administered during a campaign).

- Doses of OPV administered on or after April 1, 2016, should not be counted.

- For guidance to assess doses documented as "OPV," see www.cdc.gov/mmwr/volumes/66/wr/mm6606a7.htm?_r=0&cid=mm6606a7_w.

- For other catch-up guidance, see Table 2.

Rotavirus vaccination

(minimum age: 6 weeks)

Routine vaccination

- Rotarix**®: 2-dose series at age 2 and 4 months
- RotaTeq**®: 3-dose series at age 2, 4, and 6 months
- If any dose in the series is either **Rotarix**® or unknown, default to 3-dose series.

Catch-up vaccination

- Do not start the series on or after age 15 weeks, 0 days.
- The maximum age for the final dose is 8 months, 0 days.
- For other catch-up guidance, see Table 2.

Tetanus, diphtheria, and pertussis (Tdap) vaccination

(minimum age: 11 years for routine vaccination, 7 years for catch-up vaccination)

Routine vaccination

- Adolescents age 11–12 years:** 1 dose Tdap
- Pregnancy:** 1 dose Tdap during each pregnancy, preferably in early part of gestational weeks 27–36.
- Tdap may be administered regardless of the interval since the last tetanus- and diphtheria-toxoid-containing vaccine.

Catch-up vaccination

- Adolescents age 13–18 years who have not received Tdap:** 1 dose Tdap, then Td or Tdap booster every 10 years
- Persons age 7–18 years not fully vaccinated* with DTaP:** 1 dose Tdap as part of the catch-up series (preferably the first dose); if additional doses are needed, use Td or Tdap.
- Tdap administered at age 7–10 years:**
 - Children age 7–9 years** who receive Tdap should receive the routine Tdap dose at age 11–12 years.
 - Children age 10 years** who receive Tdap do not need the routine Tdap dose at age 11–12 years.
- DTaP inadvertently administered on or after age 7 years:**
 - Children age 7–9 years:** DTaP may count as part of catch-up series. Administer routine Tdap dose at age 11–12 years.
 - Children age 10–18 years:** Count dose of DTaP as the adolescent Tdap booster.

- For other catch-up guidance, see Table 2.

Special situations

- Wound management** in persons age 7 years or older with history of 3 or more doses of tetanus-toxoid-containing vaccine: For clean and minor wounds, administer Tdap or Td if more than 10 years since last dose of tetanus-toxoid-containing vaccine; for all other wounds, administer Tdap or Td if more than 5 years since last dose of tetanus-toxoid-containing vaccine. Tdap is preferred for persons age 11 years or older who have not previously received Tdap or whose Tdap history is unknown. If a tetanus-toxoid-containing vaccine is indicated for a pregnant adolescent, use Tdap.

- For detailed information, see www.cdc.gov/mmwr/volumes/69/wr/mm6903a5.htm.

**Fully vaccinated* = 5 valid doses of DTaP OR 4 valid doses of DTaP if dose 4 was administered at age 4 years or older

Varicella vaccination

(minimum age: 12 months)

Routine vaccination

- 2-dose series at age 12–15 months, 4–6 years
- Ensure persons age 7–18 years without evidence of immunity (see www.cdc.gov/mmwr/pdf/rr/r15604.pdf) have a 2-dose MMR at www.cdc.gov/mmwr/pdf/rr/r15604.pdf have a 2-dose series.
- Age 7–12 years:** routine interval: 3 months (a dose inadvertently administered after at least 4 weeks may be counted as valid)
- Age 13 years and older:** routine interval: 4–8 weeks (minimum interval: 4 weeks)
- The maximum age for use of MMRV is 12 years.

***Note:** For dose 1 in children age 12–47 months, it is recommended to administer MMR and varicella vaccines separately. MMRV may be used if parents or caregivers express a preference.

Catch-up vaccination

- Ensure persons age 7–18 years without evidence of immunity (see www.cdc.gov/mmwr/pdf/rr/r15604.pdf) have a 2-dose MMR at www.cdc.gov/mmwr/pdf/rr/r15604.pdf have a 2-dose series.
- Age 7–12 years:** routine interval: 3 months (a dose inadvertently administered after at least 4 weeks may be counted as valid)
- Age 13 years and older:** routine interval: 4–8 weeks (minimum interval: 4 weeks)
- The maximum age for use of MMRV is 12 years.

2/17/2022

Figure 2. (Continued)

Centers for Disease Control and Prevention | Recommended Child and Adolescent Immunization Schedule, United States, 2022

2. *Haemophilus influenzae* type b (Hib) conjugate vaccine
 - a. PedvaxHIB: Two doses (2 and 4 months)
 - b. ActHIB: Three doses (2, 4, and 6 months)
 - c. Hiberix should only be used as a booster for children 12–15 months; other formulations can be used as part of primary series.
 - d. Adverse effects: Injection-site reactions, anaphylactic reaction to vaccine component(s) possible but rare
3. Hepatitis A (Havrix, Vaqta)
 - a. Two doses: First dose at 12–23 months, second dose given at least 6 months apart
 - b. Adverse effects: Injection-site reactions, headache, anaphylaxis (rare)
4. Hepatitis B (Recombivax HB, Engerix-B)
 - a. Three doses: Birth, 1–2 months, and 6 months
 - b. Adverse effects: Injection-site reaction, fever; contraindicated in patients with anaphylactic reaction to yeast
 - c. Preterm infants from HBsAg negative mothers weighing less than 2000 g at birth should wait 1 month to receive the first dose because of their decreased immune response to the vaccine.
 - d. Infants born to HBsAg (hepatitis B surface antigen)-positive mothers should receive hepatitis B vaccine and HBIG (hepatitis B immunoglobulin) within 12 hours regardless of birth weight. Infants vaccinated at less than 2000 g require a total of 4 doses to complete the series.
 - e. Postvaccination serologic testing assesses an infant's response to HepB vaccination and typically occurs at age 9–18 months.
5. Human papillomavirus (HPV)
 - a. Age 9–14 years: Two doses at 0 and 6–12 months
 - b. Age 15 years or older: Three doses at 0, 1–2, and 6 months
 - c. Immunocompromised patients should receive three doses regardless of age at initiation of vaccine administration.
 - d. HPV9 (Gardasil 9) contains HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58. Recommended for both females and males
 - e. Adverse effects: Headache, nausea, dizziness, fainting (sit/lie down for 15 minutes after vaccine given), pain at injection site, anaphylactic reaction to yeast
6. Inactivated polio vaccine (IPV)
 - a. Typically given as part of a combination vaccine (Kinrix, Pentacel, or Pediarix). Also available as single antigen IPV (IPOL)
 - b. No serious adverse effects have been found.
7. Influenza
 - a. Formulations
 - i. IIV quadrivalent (IIV4): Fluzone, Fluarix, FluLaval, Afluria for children 6 months and older. Flucelvax for children 2 years or older
 - ii. LAIV (FluMist) for children 2 years or older
 - b. Children 6 months to 8 years
 - i. If the child has received two or more doses of trivalent or quadrivalent influenza vaccine before July 1, 2021, recommend one dose.
 - ii. If the child has not received at least two doses or if influenza immunization status is unknown, two doses given at least 4 weeks apart are recommended.
 - c. Children older than 8 years need one dose of influenza vaccine annually.
 - d. Adverse effects (IIV): Injection-site reactions, fever

- e. Adverse effects (LAIV): Nasal congestion, runny nose, fever
 - i. Contraindicated in children younger than 2 years; immunosuppressed; long-term aspirin or salicylate therapy; children 2–4 years of age who have asthma, have been labeled by a health care provider with wheezing or asthma or who have had a wheezing episode noted in the medical record within the past 12 months; Receipt of influenza antiviral medication within the previous 48 hours for oseltamivir and zanamivir, previous 5 days for peramivir, and previous 17 days for baloxavir.
 - ii. Precaution: Asthma in children 5 years and older, moderate to severe acute illness with or without fever, history of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine, chronic comorbidities (e.g., renal, hepatic, cardiovascular, neurologic)
- f. Except for the cell culture based inactivated influenza vaccine (Flucelvax), all influenza vaccines contain a very small amount of ovalbumin (egg protein). The Advisory Committee on Immunization Practices (ACIP) recommendations state that individuals with a history of egg allergy of any severity may receive any licensed, recommended, and age-appropriate influenza vaccine (IIV or LAIV).
- g. Approach to children with egg allergy (ACIP recommendations):
 - i. Individuals with a history of egg allergy who have experienced only urticaria (hives) after exposure to eggs should receive influenza vaccine.
 - ii. If a more serious reaction occurs (angioedema, respiratory distress, lightheadedness, repeated emesis, history of epinephrine use), vaccine should be administered in an inpatient or outpatient medical setting and supervised by a health care provider who can recognize and manage severe allergic conditions.
 - iii. If a child develops a severe allergic reaction to influenza vaccine, do not administer again.
- 8. MMR – Live attenuated
 - a. Two doses: 12–15 months and 4–6 years
 - b. Adverse effects: Fever (7–14 days after vaccination), transient rash, arthralgias (1–3 weeks after vaccination, females > males), febrile seizures, thrombocytopenia (rare), administration of blood products or immunoglobulin can block host response (depending on the product/dose, needs to be separated anytime at 3–11 months)
 - c. Contraindicated in patients who are immunosuppressed, HIV with CD4 count less than 15% (or less than 200 cells/mm³ if older than 5 years), anaphylactic reaction to neomycin, pregnancy
 - d. Individuals previously vaccinated with two doses who are identified by public health authorities as being part of a group or population at an increased risk of acquiring mumps because of an outbreak should receive a third dose of a mumps virus–containing vaccine to improve protection against mumps disease and related complications.
- 9. Meningococcal vaccine
 - a. Different meningococcal serogroups exist. The most common serotypes in the United States are B, C, and Y.
 - b. A quadrivalent conjugate vaccine against meningococcus serogroups A, C, Y, and W135 conjugated to diphtheria toxin (MenACWY-D or Menactra) or conjugated to a mutant diphtheria toxin (MenACWY-CRM or Menveo). Two doses: 11–12 years, 16 years
 - c. Meningococcal group B vaccine:
 - i. Typically considered in two patient groups
 - (a) Routine vaccination of persons aged 10 years or older with certain medical conditions, such as anatomic or functional asplenia, complement component deficiencies, or complement inhibitor use
 - (b) Possible vaccination of persons aged 16–23 years should be determined on the basis of shared clinical decision-making. Patients at risk are typically college students living on-campus.

- ii. MenB-FHbp (Trumenba): Give three doses at 0, 1–2, and 6 months to individuals (10 years and older) with qualifying medical conditions. Give two doses at 0 and 6 months to healthy adolescents (16–23 years) (i.e., college students)
 - iii. MenB-4C (Bexsero): Two doses at least 1 month apart for individuals 10–25 years of age
 - iv. MenB-FHbp and MenB-4C are NOT interchangeable.
 - v. Adverse effects: Injection-site reactions, fever, fatigue, headache, arthralgias
10. Pneumococcal vaccine
- a. Pneumococcal conjugate vaccine (PCV13) or Prevnar 13 – Four doses (2, 4, 6, 12–15 months)
 - b. PPSV23 (pneumococcal polysaccharide) or Pneumovax 23 – Recommended for children 2 years and older with high-risk conditions: Immunosuppression, asplenia, sickle cell disease, CSF leak, cochlear implant, chronic heart/lung/liver/kidney disease, or diabetes. Children older than 2 years with these high-risk conditions who have been incompletely immunized usually need to receive PCV13 first.
 - c. Adverse effects: Injection-site reactions, irritability, fever, decreased appetite
11. Rotavirus – Oral vaccine; live attenuated
- a. Rotarix (RV1) – Two doses at 2 and 4 months, or
 - b. RotaTeq (RV5) – Three doses at 2, 4, and 6 months
 - c. Adverse effects: Intussusception (rare), anaphylactic reaction to latex (RV1 vaccine)
12. Varicella (Varivax) – Live attenuated
- a. Two doses: 12–15 months and 4–6 years
 - b. Adverse effects: Injection-site pain/redness, fever, rash (local or generalized); administration of blood products or immunoglobulin can block host response (depending on the product, needs to be separated anytime at 3–11 months)
 - c. Measles, mumps, rubella, and varicella (MMRV) combination vaccine (ProQuad) is associated with higher rates of fever and febrile seizures at 5–12 days after vaccination than are MMR and Varivax administered at separate sites/times.
 - d. Contraindicated in patients who are immunosuppressed, HIV with CD4 count less than 15% (or less than 200 cells/mm³ if older than 5 years), anaphylactic reaction to neomycin or gelatin, pregnancy, temperature greater than 101.3°F (38.5°C)
13. COVID-19 – mRNA vaccine – Due to the rapidly changing nature of this topic, please refer to www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html for up-to-date information.

D. Combination Products

- 1. Kinrix (DTaP plus IPV): One dose (4–6 years)
- 2. Pentacel (DTaP plus IPV plus Hib): Four doses (2, 4, 6, and 15–18 months)
- 3. Pediarix (DTaP plus IPV plus hepatitis B vaccine): Three doses (2, 4, and 6 months)
- 4. Comvax (Hib plus hepatitis B vaccine): Two doses (2 and 4 months)
- 5. Menhibrix (meningococcal plus Hib): Three doses (2, 4, and 6 months)
- 6. ProQuad (MMR plus varicella): Two doses (12–15 months, 4–6 years)
- 7. Quadracel (DTaP plus IPV) (4–6 years)
- 8. Vaxelis (DTaP plus IPV plus Hib plus hepatitis B): Three doses (2, 4, and 6 months)

Table 4. Summary of Inactivated and Live Vaccines

Inactivated Vaccines	Live Vaccines
DTaP/Tdap	Influenza (intranasal)
Hib	MMR
Hepatitis B	Rotavirus
Hepatitis A	Typhoid (oral)
HPV	Varicella
Influenza (IM)	
Japanese encephalitis	
Meningococcal	
Pneumococcal	
Polio	
Rabies	
Typhoid (IM)	
Herpes zoster (Zostavax)	

HPV = human papillomavirus; IM = intramuscular(ly).

E. Other General Points About Vaccinations:

1. Avoid live vaccines in pregnancy.
2. Avoid live vaccines in immunosuppressed individuals.
 - a. Combined primary immunodeficiency
 - b. Receiving cancer chemotherapy
 - c. Recent HCT
 - d. Receiving biologic agents (e.g., TNF inhibitors, rituximab)
 - e. HIV infection – Depends on the vaccine
 - i. Avoid MMR and varicella vaccines if the CD4 count is less than 15% (less than 200 cells/mm³ if older than 5 years).
 - ii. Avoid LAIV and MMRV, regardless of the CD4 count.
 - iii. Rotavirus is OK to give: Weak recommendation in patients with low CD4 count, so clinical judgment is advised
 - f. Receiving daily corticosteroid therapy with a dose of 20 mg or greater (or greater than 2 mg/kg/day if weight is less than 10 kg) of prednisone or equivalent for 14 days or more
3. Avoid all vaccines in moderate/severe illness.
4. Anaphylactic reaction (IgE mediated) to a vaccine component is very rare and a contraindication for further doses. Can be caused by the immunizing agent or, more commonly, an inert ingredient (gelatin, egg, latex, yeast). Skin testing by an allergist is recommended to identify the cause of the allergic reaction.
5. Comfort measures to reduce pain during injection:
 - a. Nonpharmacologic: Breastfeeding during vaccination if infant is nursing, pacifier use, distraction
 - b. Pharmacologic: Cooling spray or topical anesthetic applied just before the injection

F. All 50 U.S. states require some immunizations for school entry. However, parents can elect to exempt their children from immunizations. There are three types of exemptions:

1. Medical exemptions – Valid medical contraindication to a vaccine or vaccine component (all 50 states)
2. Religious exemptions – Religious beliefs oppose immunizations (most states allow)
3. Philosophical exemptions – Personal, moral, or philosophic belief against some or all immunizations (about 40% of states allow). Six states (California, Connecticut, Maine, Mississippi, New York, and West Virginia) do NOT accept religious or philosophical exemptions.

G. Common Parental Concerns

1. Pain from the injection, fevers: Mild and temporary, supportive management
2. Too many vaccines are overwhelming to the immune system: No evidence; immune system can respond to many antigens
3. Thimerosal (ethylmercury) and risk of autism: Population studies show no relationship. Studies showed that the incidence of autism increased in California, Canada, and Denmark after thimerosal was removed from vaccines.
4. MMR and risk of autism: Scientifically disproven
5. Is vaccination really necessary? Low incidence of vaccination-preventable illnesses and awareness of significant health threat
6. Better to acquire immunity “naturally” than through vaccination (e.g., many parents remember having varicella as children and are not aware of potentially serious complications)

Patient Case

6. For which patient would it be best to withhold vaccination until a later date?
 - A. MMR for a 6-year-old girl receiving etanercept for JIA.
 - B. MMR for a 6-year-old boy with HIV and a CD4 count of 650 cells/mm³.
 - C. Inactivated flu vaccine for a 1-year-old with otitis media.
 - D. Tdap for a pregnant 17-year-old female adolescent.

V. ANAPHYLAXIS

- A. Definition: A severe, potentially life-threatening generalized or systemic hypersensitivity reaction. Can be immunologic (IgE-dependent or IgE-independent), nonimmunologic, or idiopathic
- B. Epidemiology: Unknown; possible lifetime prevalence estimated to be 0.05%–2%
- C. Pathophysiology and Associated Triggers:
 1. IgE-mediated (most common): Allergen interacts with allergen-specific IgE bound to mast cells/basophils; causes degranulation, release, and production of mediators and cytokines (TNF, histamine, tryptase)
 - a. Foods (e.g., nuts, fish, egg, milk)
 - b. Insect stings (Hymenoptera family: honeybees, bumblebees, wasps, hornets, fire ants)
 - c. Medications (e.g., β -lactams, especially penicillin; aspirin, NSAIDs, monoclonal antibodies), latex
 2. IgE-independent
 - a. Mechanisms generally not well understood; may be IgG mediated or involve immune complex–complement mediated reactions. Examples include omalizumab and hemodialysis membrane.
 - b. Disturbance in arachidonic acid metabolism: Aspirin, NSAIDs
 3. Nonimmunologic: Direct activation of mast cells/basophils with resulting histamine release
 - a. Exercise, cold
 - b. Drugs (e.g., opioids)
- D. Common Signs and Symptoms:
 1. Skin (about 90%) – Hives, itching, flushing, swollen lips-tongue-uvula, periorbital edema, conjunctival swelling
 2. Respiratory (about 70%) – Nasal discharge, nasal congestion, change in voice quality, sensation of throat closure or choking, stridor, shortness of breath, wheeze, cough, respiratory failure

3. GI (about 45%) – Nausea/vomiting, diarrhea, cramps
 4. Cardiovascular (about 45%) – Dizziness, tachycardia, hypotension (and cardiovascular collapse)
- E. Anaphylaxis is likely if any of the following three criteria are met:
1. Acute onset of illness with involvement of the skin, mucosal tissue, or both and at least one of the following:
 - a. Respiratory compromise
 - b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
 2. Two or more of the following that occur rapidly after exposure to a likely allergen:
 - a. Involvement of the skin or mucosal tissue
 - b. Respiratory compromise
 - c. Reduced blood pressure or associated symptoms
 - d. Persistent gastrointestinal symptoms
 3. Reduced blood pressure after exposure to known allergen
 - a. Low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure. (Note: Per guideline definition, low systolic blood pressure for children is defined as <70 mmHg from 1 month to 1 year, <(70 mmHg + [2 × age]) from 1 to 10 years, and <90 mmHg from 11 to 17 years).

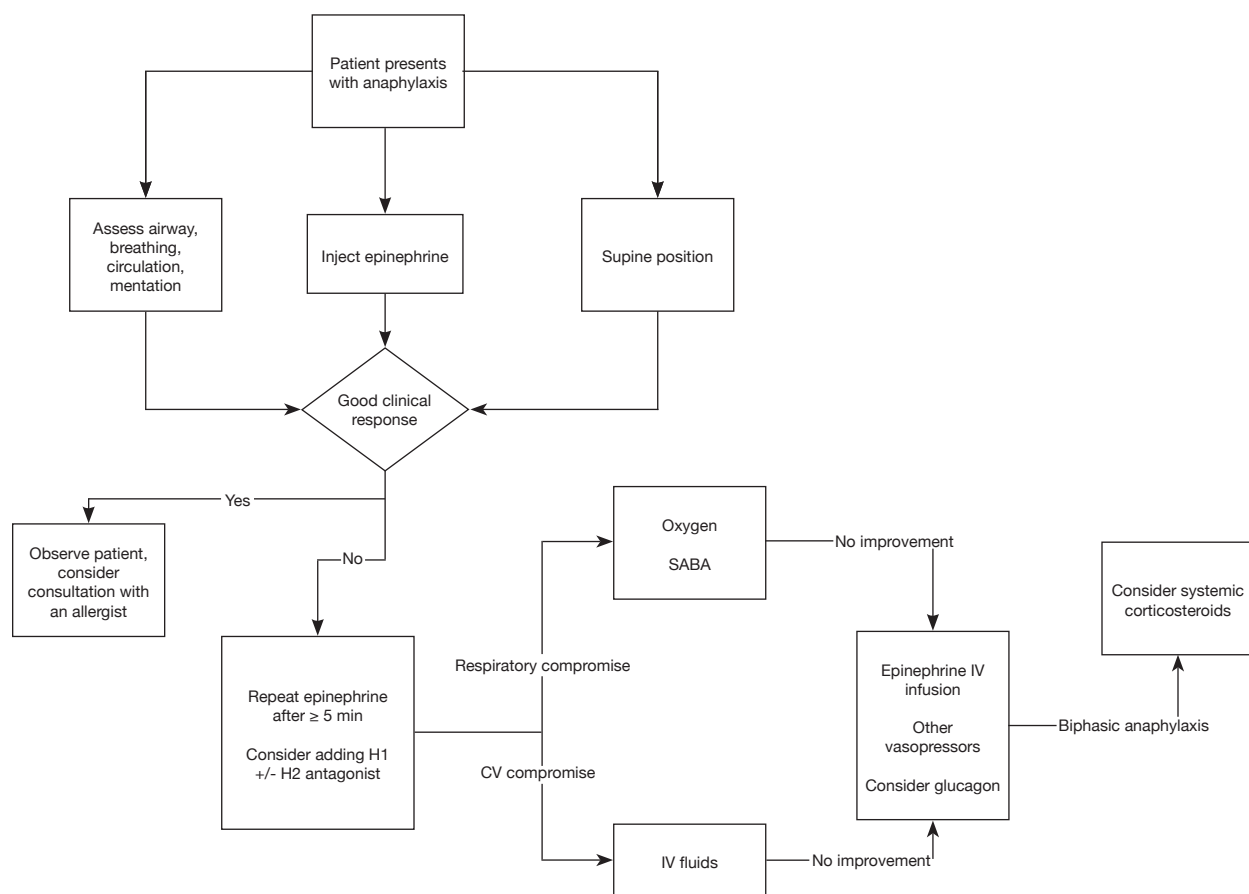


Figure 3. Algorithm for the treatment of anaphylaxis.

CV = cardiovascular; H = histamine; IV = intravenous(Iy); SABA = short-acting β_2 -agonist.

- F. The course of anaphylaxis varies among individuals and is impossible to predict. Anaphylaxis may be mild and resolve spontaneously, or it may be severe and progress to respiratory or cardiovascular compromise and death. Because it is impossible to predict the course, epinephrine should be given in a timely manner.
1. Biphasic anaphylaxis – Second recurrence of symptoms without additional allergen exposure usually 8–10 hours after resolution of the initial anaphylactic episode with no additional exposure to the trigger. May occur in up to 11% of children with anaphylaxis
 2. Protracted anaphylaxis – Anaphylactic reaction that lasts for hours or days
- G. Comorbidities/Cofactors That Increase the Severity of the Allergic Reaction: Pulmonary disease (including asthma), cardiovascular disease, physical exertion, alcohol, NSAIDs, infection, stress, adolescence
- H. Acute Treatment (Figure 3)
1. Epinephrine
 - a. Considered first-line treatment for anaphylaxis
 - b. Dose: 1:1000 (1 mg/mL), 0.01 mg/kg (max 0.3 mg) intramuscularly or autoinjector (e.g., Auvi-Q, EpiPen Jr, Jext) 0.15 mg (weight 7.5–25 kg), 0.3 mg (weight greater than 25 kg), administered into the mid-outer thigh. Wait at least 5 minutes to repeat.
 - c. Intramuscular administration is usually preferred to subcutaneous administration because of the faster increase in serum concentration.
 - d. If inadequate response to two or more intramuscular injections, give epinephrine by intravenous continuous infusion (ICU with frequent cardiac monitoring required)
 - e. Adverse effects: Anxiety, restlessness, palpitations, tremor, cardiovascular effects (ventricular arrhythmia, angina, myocardial infarction) at high doses. There is no contraindication to epinephrine in suspected anaphylaxis.
 2. Removal of the trigger, if possible
 3. Oxygen (intubation if respiratory arrest)
 4. Posture: Supine position with legs elevated
 5. Intravenous access and normal saline administration (up to 30 mL/kg in the first hour) if cardiovascular instability present
 6. Glucagon
 - a. Mechanism of action: Inotropic and chronotropic effects not mediated through β -receptors
 - b. Recommended for patients taking β -blockers who do not respond to epinephrine
 - c. Dose: 20–30 mcg/kg (max 1 mg) intravenously over 5 minutes; can be repeated or followed by an infusion
 7. Histamine-1 (H_1)-antagonists
 - a. Mechanism of action: Inhibit action of histamine by binding to H_1 -receptors
 - b. Only relieve itch and hives; should **never** be used in initial management of suspected anaphylaxis
 - c. For example, diphenhydramine (Benadryl) 1 mg/kg intravenously or orally (max 50 mg). Second-generation H_1 antihistamines are less sedating but are only available orally.
 - d. Sometimes, an H_1 antihistamine is combined with an H_2 antihistamine for additive response (e.g., ranitidine 1 mg/kg intravenously [max 50 mg] over 10–15 minutes or famotidine 0.25 mg/kg [max 20 mg] intravenous push).
 - e. Adverse effects: Hypotension, sedation
 8. Other adjunctive therapies
 - a. Nebulized short-acting β -agonists (albuterol, levalbuterol) for bronchospasm unresponsive to epinephrine
 - b. Systemic corticosteroids may decrease the risk of biphasic anaphylaxis.
 - c. Vasopressors such as dopamine for refractory hypotension

Patient Case

7. A previously healthy 6-year-old boy (weight 20 kg [44 lb]) is brought to the ED after being stung on his arm by a bee. He initially had localized pain and swelling. However, 15 minutes later, he begins to have shortness of breath, and his parents see him wheezing. His physical examination is notable for generalized urticaria, and his vital signs are as follows: respiratory rate 39 breaths/minute, blood pressure 65/38 mm Hg, heart rate 131 beats/minute, and temperature 98.6°F (37.0°C). The physician on duty would like to administer epinephrine. Which is most appropriate to recommend for this patient?
- A. Epinephrine (1 mg/mL) 0.2 mL given intramuscularly once.
 - B. Epinephrine (1 mg/mL) 0.4 mL given intramuscularly once.
 - C. Epinephrine (0.1 mg/mL) 0.2 mL given intramuscularly once.
 - D. Epinephrine 0.1-mcg/kg/minute intravenous infusion.

I. Prevention

- 1. Education on allergen avoidance, cross-reactivity between drugs
- 2. Education on use of epinephrine autoinjector: why to carry two, keep with you at all times as previous reactions do not dictate/predict future reactions, proper storage, how to access assistance programs, trainer devices, counsel on biphasic reactions
- 3. Medical identification (bracelet, wallet card)
- 4. Immunotherapy
- 5. Desensitization

J. Drug Desensitization

- 1. Drug desensitization is the induction of a temporary state of tolerance to a drug responsible for a hyper-sensitivity reaction, and this state can only be maintained by continuous administration of the medication. Drug desensitization is indicated if a certain drug that the patient is allergic to is either irreplaceable or more effective than other alternatives.
- 2. The exact mechanism by which desensitization works is unknown, but it is thought to work because IgE is neutralized by the increasing dose of antigen or because mast cells are slowly degranulated, thus provoking milder reactions.
- 3. Increasing doses of the drug over a short period are administered until the cumulative therapeutic dose is achieved and tolerated. Usually initiated at 1/10,000–1/1,000,000 of the therapeutic dose and gradually increased. Depending on the severity of the reaction, the patient may need to be hospitalized for the procedure.
- 4. Tolerance is lost once the drug is discontinued, and the patient will need to be desensitized again.
- 5. Contraindications: Uncontrolled cardiovascular disease, uncontrolled asthma, hemodynamic instability, history of severe immunocytotoxic reactions, vasculitis, or bullous skin disease (Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms [DRESS])
- 6. Adverse effects:
 - a. Breakthrough reactions – Most likely to occur at the end of the procedure; may resolve on their own once the desensitization is interrupted. If not, can be treated with antihistamines, bronchodilators, or epinephrine
 - b. Depending on the severity of reaction (laryngeal edema, hypotension), desensitization may need to be aborted – Clinical judgment should be used.
- 7. Many protocols exist in the literature (see Exp Review Clin Immunol 2020;16:91-100; Pediatr Allergy Immunol 2013;24:3-9 for sample protocols).

Patient Case

8. A 17-year-old male adolescent presents to the pediatric clinic for a follow-up after being discharged from the hospital on a continuous infusion of penicillin for the treatment of neurosyphilis. During hospitalization, the patient underwent penicillin desensitization because of his history of anaphylaxis to penicillin. However, once the patient was discharged, he claims he could not obtain intravenous penicillin and has not received it since his discharge 3 days ago. Which would best be recommended to treat the patient's infection?
- A. Reinitiation of penicillin continuous infusion to complete therapy.
 - B. Readmission to the hospital to repeat desensitization.
 - C. Reinitiation of penicillin to complete therapy, but change it to the oral route.
 - D. Reinitiation of penicillin continuous infusion, and premedicate patient with an antihistamine before each infusion.

VI. FOOD ALLERGIES

- A. Definition: Adverse health effect arising from a specific immune response that occurs reproducibly upon exposure to a given food
- B. Food allergies are immune-mediated reactions and should not be confused with food intolerance (e.g., lactose intolerance), which is not immune-mediated.
 - 1. IgE-mediated: GI hypersensitivity, pollen food allergy syndrome, exercise-induced anaphylaxis triggered by food
 - 2. Non-IgE-mediated: Food protein-induced enterocolitis or proctitis
 - 3. Mixed IgE and non-IgE: Eosinophilic esophagitis, eosinophilic gastroenteritis
- C. Epidemiology:
 - 1. Food allergies are over-reported by patients, and a true diagnosis requires additional objective measures in addition to symptoms. One study found that self- or parent-reported allergy in children was about 12%, but the actual prevalence confirmed with diagnostic testing was 3%.
 - 2. Eight most common childhood allergies: Milk, eggs, fish, shellfish, peanuts, tree nuts, soy, and wheat. Sometimes these allergens may be present as excipients in pharmaceutical products or cosmetic product ingredients. Due to variability in the amounts of these ingredients within products, as well as variability in susceptibility among individual patients, it is hard to predict whether an allergic reaction will occur or not. Overall, it appears that reactions are uncommon.
 - 3. Children with concurrent atopic dermatitis or asthma have a much higher prevalence of food allergies of 30%–45%.
- D. Onset: If IgE-mediated food allergy, onset occurs within minutes to a few hours. A delayed reaction of hours to days typically occurs in non-IgE or mixed reactions.
- E. Symptoms of IgE-Mediated Food Allergies:
 - 1. Cutaneous: Erythema, pruritus, urticaria, morbilliform eruption, angioedema
 - 2. Ocular: Pruritus, conjunctival erythema, tearing, periorbital edema
 - 3. Upper respiratory: Nasal congestion, rhinorrhea, sneezing, pruritus, laryngeal edema, hoarseness
 - 4. Lower respiratory: Cough, chest tightness, dyspnea, wheezing, accessory muscle use
 - 5. GI: Angioedema of lips/tongue/palate, nausea, vomiting, abdominal pain, diarrhea, reflux
 - 6. Cardiovascular: Tachy- or bradycardia, hypotension, dizziness, fainting

F. Diagnosis of IgE-Mediated Food Allergy

1. Medical history
2. Skin prick test
 - a. Noninvasive
 - b. Detects the presence of IgE bound to the surface of cutaneous mast cells; positive test shows up as a wheal
 - c. Provides results within 30 minutes but with low sensitivity (50%–60%)
 - d. Drugs that interfere with the results: Antihistamines (should be held about 1 week before testing), topical steroids, H₂-receptor antagonists, tricyclic antidepressants
3. Measurement of allergen-specific serum IgE (total serum IgE is not recommended). High initial IgE concentrations correlate with disease persistence into adulthood but not with severity of reaction.
4. Note: Diagnosis should not be made with a skin prick test or allergen-specific serum IgE alone – Many children may have a positive result (which indicates sensitization) but may be able to tolerate the specific food allergen.
5. Oral food challenge. Double-blind placebo-controlled oral food challenge is considered the gold standard. If not feasible, single-blind and open-food challenge may be used. In patients with known severe anaphylaxis, oral food challenge is usually not done.

G. Egg Allergy

1. Usually presents in the first year of life
 - a. 70% of children who are allergic to eggs tolerate baked eggs.
 - b. 70%–80% of children with egg allergy will outgrow it by age 16.
2. Medications that contain egg
 - a. Propofol – Contains egg lecithin. One study found that most children with egg allergy will tolerate it, but anaphylaxis has been reported. For those with a history of anaphylaxis to eggs, changing to an alternative agent or administering a test dose may be appropriate.
 - b. Intralipid – Contains egg yolk phospholipids. Allergic reactions are uncommon (one case report of urticaria). Omegaven (fish oil emulsion) and Smoflipid (soybean oil, olive oil, and fish oil emulsion) are alternatives, but they also contain very small amounts of egg protein.
3. Childhood routine vaccines that contain egg protein
 - a. MMR – Safe in all children with egg allergy
 - b. Influenza – ACIP recommends that individuals with a history of egg allergy of any severity should receive any licensed, recommended, and age-appropriate influenza vaccine (IIV, RIV4, or LAIV4).

H. Cow's Milk Protein Allergy

1. Most children will be given a diagnosis during infancy. Most will outgrow the allergy (80% by age 5).
2. Cross-reactivity
 - a. Breastfed infants can react if the mother ingests/eats dairy products or those that contain milk protein – yogurt, butter, milk, cheese.
 - b. 10%–15% of children allergic to milk are also allergic to soy.
 - c. Most will have a cross-reactivity to mammalian milk (e.g., goats, sheep).
3. Treatment
 - a. If breastfeeding, the mother should eliminate dairy products from her diet.
 - b. If formula-fed
 - i. Infants with mild to moderate allergy symptoms will usually be changed to an extensively hydrolyzed casein-based formula that is based on cow's milk but extensively broken down into smaller peptides and less likely to be recognized by the immune system.
 - ii. Infants with severe allergy symptoms are usually changed to an amino acid formula.

- iii. Soy formula may be an option. However, there is a risk of cross-reactivity, and soy should be avoided in children younger than 6 months because of the presence of isoflavones (and their estrogenic effects).

I. Peanut and/or Tree Nut Allergy

1. Examples of tree nuts: Walnut, almond, hazelnut, cashew, pistachio
2. Cross-sensitivity is common.
 - a. About 25%–50% of children with a peanut allergy have a tree nut allergy.
 - b. About 50% of children with an allergy to tree nuts are allergic to more than one nut.
 - c. Cross-sensitivity to legumes (soy, chickpea, lentils, etc.) is commonly found on IgE antibody testing but rarely leads to clinical reactions.
 - d. Only 10%–20% of children “outgrow” the allergy.
3. More likely to cause severe allergic reactions than other common food allergens. Adolescents with unintended exposure are at a particularly high risk of death.
4. Other atopic diseases are particularly common: 50%–75% of children with a peanut/tree nut allergy have asthma, eczema, and/or allergic rhinitis.
5. Primary prevention: Early introduction of peanut-containing food before age 12 months reduces the development of peanut allergy by 81%. Updated guidelines now recommend early introduction (4–6 months of age) of peanut-containing foods, particularly in infants with eczema and/or egg allergy, because they are at a high risk of developing a peanut allergy later in life.

J. Fish and Shellfish Allergy

1. Allergy usually persists into adulthood.
2. More common diagnosis among adolescents and adults
3. Cross-reactivity
 - a. Patients with fish and shellfish allergy usually do not cross-react because different allergens are involved.
 - b. Patients with allergy to one fish are at higher risk of being allergic to another fish. Similarly, patients with allergy to one type of shellfish have a high risk of being allergic to another type of shellfish.
 - c. Patients with shellfish allergy are more likely to be allergic to dust mites/cockroaches because of the similarity of allergens involved.

K. General Treatment Strategies

1. Secondary prevention
 - a. Avoidance of the culprit foods – Can be difficult in patients with egg or milk allergy because these are ubiquitous in many foods
 - b. Patient/caregiver education
 - i. How to read food labels
 - ii. Cross-contact and hidden ingredients: Contamination of “safe” food with a small amount of allergenic food (restaurants, bakeries)
 - iii. Symptom recognition and management
 - iv. Support groups and educational resources
 - c. Dietitian referral
 - d. Food allergy action plan
 - i. Describes what to do if allergen is involuntarily ingested
 - ii. Describes what symptoms justify use of an epinephrine autoinjector versus antihistamine
2. Anaphylactic reactions should be treated as described in the Anaphylaxis section of the review.

3. Symptomatic treatment of mild to moderate symptoms (e.g., urticaria, angioedema, wheezing). Important to keep in mind that these treatments do not substitute epinephrine use
 - a. Second-generation with or without first-generation H₁-antagonist (e.g., cetirizine 2.5 mg orally daily if older than 6 months [max 5 mg in children 1–5 years] and 5–10 mg orally daily if 6 years and older)
 - b. Short course of systemic steroids (e.g., prednisolone 0.5–1 mg/kg/day [max 60 mg] tapered over 5–7 days); may be beneficial in patients with persistent bronchospasms after initial resolution of anaphylaxis
 - c. Short-acting β_2 -agonists (e.g., albuterol 0.15 mg/kg nebulized; repeat as needed) for persistent bronchospasms after administration of epinephrine
4. Oral immunotherapy: Induction of tolerance to the culprit food by introducing small amounts (started under clinical supervision) and slowly increasing them to a regular serving size
 - a. Patients need to continue taking in the foods on a regular basis to maintain tolerance.
 - b. Peanut allergen oral immunotherapy powder (Palforzia)
 - i. FDA approved in January 2020 for mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in patients with a confirmed diagnosis of peanut allergy
 - ii. Administered on a titration schedule until target maintenance dose (300 mg) is reached
 - iii. Black box warning: Anaphylaxis – must be dispensed with epinephrine injector
 - iv. Only available through REMS (Risk Evaluation and Mitigation Strategies) program

Patient Case

Questions 9 and 10 pertain to the following case.

A 5-year-old boy presents to the pediatric clinic after treatment with epinephrine in the ED for acute development of coughing, wheezing, urticaria, and periorbital edema after a presumably first-time ingestion of almonds.

9. Which medication would best be prescribed for use in case of an involuntary ingestion in the future?
 - A. Diphenhydramine.
 - B. Prednisone.
 - C. Epinephrine.
 - D. Albuterol.
10. Which is the best management strategy for this child's presumptive almond allergy?
 - A. Avoid foods that contain almonds.
 - B. Try small amounts of almonds to see if the child will tolerate this.
 - C. Avoid almonds for now, but try almonds again in a few years because patient will likely “grow out of it.”
 - D. Take cetirizine before consuming any almond-containing foods.

VII. ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

- A. Epidemiology:
 1. Major cause of cardiovascular death in children and young adults in developing countries
 - i. Global incidence in children 5–14 years of age is 300,000–350,000 per year.
 - ii. Highest prevalence in sub-Saharan Africa and indigenous Australia

2. Uncommon in the United States
 3. Mainly affects children 5–15 years of age
- B. Pathophysiology: Group A *Streptococcus* (GAS) pharyngitis may lead to acute rheumatic fever and carditis.
1. Genetic predisposition – Molecular mechanism is unknown, but patients with a family history of acute rheumatic fever are at a significantly higher risk of developing the same disease.
 2. Antigenic mimicry – Antibodies against GAS react with several cardiac proteins such as cardiac myosin and tropomyosin.
- C. Risk Factors: Poverty, overcrowding, malnutrition
- D. Acute Rheumatic Fever:
1. Usually occurs about 3 weeks after GAS pharyngitis
 2. Can affect many systems (musculoskeletal, CNS, skin, heart). Except for the heart, organs are usually transiently affected.
- E. Diagnosis of Acute Rheumatic Fever (Jones criteria) – Diagnosis is made if the patient meets two major criteria, or one major and two minor criteria if the history includes a preceding streptococcal infection.
1. Major criteria
 - a. Migratory arthritis
 - i. Inflammation affecting several joints in quick succession; very painful
 - ii. Knees, ankles, elbows, and wrists are most commonly affected.
 - iii. Usually first and most prominent symptom of acute rheumatic fever; lasts about 2 weeks
 - iv. Patients taking NSAIDs may have fewer symptoms.
 - b. Carditis and valvulitis
 - i. Develops in about 50%–70% of individuals with acute rheumatic fever
 - ii. Valvular heart disease: Mitral regurgitation (almost 100%) with or without aortic regurgitation (20%–30%) – Can lead to mitral stenosis and other cardiovascular complications (e.g., atrial fibrillation, thromboembolic disease)
 - iii. Carditis: Pericarditis, myocarditis
 - c. Sydenham chorea (St. Vitus dance)
 - i. Usually begins 1–6 months after the onset of acute rheumatic fever in 10%–30% of individuals
 - ii. Symptoms include chorea (distal movements of the hands, rapid irregular jerking of the face and feet), muscle weakness and loss of fine motor control, and psychiatric changes (emotional lability, irritability, obsessive-compulsive symptoms).
 - d. Erythema marginatum
 - i. Pink or faintly red, nonpruritic rash involving the trunk and sometimes the limbs; lesions may appear, disappear, and reappear in a matter of hours
 - ii. Incidence less than 6%
 - iii. Usually occurs early in the course of disease in patients with carditis; rare if no carditis present
 - e. Subcutaneous nodules
 - i. Firm, painless lesions usually located over a bony surface or near tendons
 - ii. Incidence less than 10%
 - iii. Usually appear after the first weeks of illness, usually in patients with relatively severe carditis
 2. Minor criteria:
 - a. Arthralgia
 - b. Fever (temperature 101.3°F [38.5°C] or higher)
 - c. Elevated erythrocyte sedimentation rate, CRP
 - d. Prolonged PR interval (after accounting for age variability)

F. Primary Prevention of Acute Rheumatic Fever

1. Recognition of GAS pharyngitis
 - a. Signs and symptoms: Sudden-onset sore throat, dysphagia, fever, scarlet fever rash, headache, nausea/vomiting, tonsillopharyngeal erythema and/or exudates, beefy/red/swollen uvula, tender/enlarged anterior cervical nodes
 - b. Throat swab, followed by either throat culture or rapid antigen detection test
 - c. Testing is usually not recommended for children younger than 3 years because GAS pharyngitis is rare (unless confirmed exposure).
2. Treatment of GAS pharyngitis with antibiotics (Table 5). Penicillin is the therapy of choice because it has well-documented efficacy and no reports of resistance. For children allergic to penicillin, oral cephalosporins or clindamycin is an alternative.

G. Secondary Prevention of Acute Rheumatic Fever

1. Preventing recurrent infection is the most effective way to prevent the development of severe rheumatic heart disease.
2. Benzathine penicillin G is preferred because nonadherence is the main cause of treatment failure (Table 6).

H. Other Treatments

1. Arthritis: NSAIDs until clinical improvement and inflammatory markers have normalized. Traditionally, aspirin 80–100 mg/kg/day in divided doses every 4–6 hours has been used. Some clinicians prefer other NSAIDs because of their less frequent dosing and fewer adverse effects (e.g., naproxen 10–20 mg/kg/day in divided doses every 12 hours).
2. Carditis: Management of heart failure, initiation of antibiotics for secondary prophylaxis. Some experts recommend systemic corticosteroids in patients with severe disease.

Table 5. Primary Prevention of Acute Rheumatic Fever

Drug	Dose	Duration (days)
Penicillin V potassium (Truxcillin VK)	250 mg PO BID-TID (≤ 27 kg), or 500 mg PO BID-TID (> 27 kg)	10
Amoxicillin (Amoxil, Trimox)	50 mg/kg PO QD (max 1 g)	10
Benzathine penicillin G (Bicillin LA)	600,000 units IM (≤ 27 kg) or 1,200,000 units IM (> 27 kg)	Once
Cephalexin ^a (Keflex)	20 mg/kg (max 500 mg) PO BID	10
Clindamycin (Cleocin)	7 mg/kg (max 300 mg) PO TID	10
Azithromycin (Zithromax)	12 mg/kg (max 500 mg) PO QD	5
Clarithromycin (Biaxin)	7.5 mg/kg (max 250 mg) PO BID	10

^aOther oral cephalosporins are also acceptable.

BID = twice daily; PO = oral(ly); QD = once daily; TID = three times daily.

Table 6. Secondary Prevention of Acute Rheumatic Fever

Drug	Dose	Duration
Penicillin V potassium (Truxcillin VK)	250 mg PO BID	No carditis: 5 yr or until 21 yr of age (whichever is longer); carditis with no valvular disease: 10 yr or until 21 yr of age (whichever is longer); carditis with valvular disease: 10 yr or until 40 yr of age (whichever is longer); sometimes lifelong
Benzathine penicillin G (Bicillin LA)	600,000 units IM x 1 (≤ 27 kg), or 1,200,000 units IM (> 27 kg) every 3–4 wk	
Azithromycin	5 mg/kg PO QD (max 250 mg)	

Patient Case

Questions 11 and 12 pertain to the following case.

A 9-year-old girl with a medical history of rheumatic heart disease presents with progressive breathlessness and fever for 10 days. In 2011, she was given a diagnosis of acute rheumatic fever with mitral regurgitation and was prescribed oral penicillin, but she admits that she has not taken it for several months. Her chest radiograph reveals cardiomegaly, whereas a TEE (transesophageal echocardiography) reveals a dilated left ventricle, severe mitral regurgitation, moderate aortic regurgitation, mild tricuspid regurgitation, and an ejection fraction of 65%. Physical examination does not reveal any musculoskeletal or CNS disease. She is given a diagnosis of recurrent acute rheumatic fever and congestive heart failure.

11. Which regimen would best be recommended for the secondary prevention of acute rheumatic fever?
 - A. Penicillin V potassium.
 - B. Benzathine penicillin G.
 - C. Erythromycin.
 - D. Clindamycin.
12. Which is the most appropriate duration of secondary antimicrobial prophylaxis for this patient?
 - A. At least 5 years.
 - B. At least 10 years.
 - C. At least until she is 21 years of age.
 - D. At least until she is 40 years of age.

VIII. SYSTEMIC LUPUS ERYTHEMATOSUS

- A. Epidemiology: Estimated to affect 5000–10,000 children in the United States
 1. Racial differences: White < Hispanic < African Americans < Asians
 2. Sex differences: Females > males
 3. Most patients develop disease after 8 years of age.
- B. Clinical Features: Essentially the same disease as adult systemic lupus erythematosus (SLE) with the same classification criteria. However, tends to be more aggressive and have more renal and neurologic complications
 1. Constitutional: Fever, malaise, weight loss
 2. Cutaneous: Malar rash, discoid rash, alopecia, photosensitivity, generalized rash

3. Musculoskeletal: Myalgia, arthralgia
 4. Cardiac: Pericarditis with or without effusion, myocarditis, atherosclerosis
 5. Pulmonary: Pleurisy with or without effusion, thromboembolism
 6. Vascular: Raynaud phenomenon, vasculitis
 7. GI: Oral ulcerations, anorexia, nausea, vomiting, peritonitis, GI vasculitis
 8. Neurologic: Psychosis, seizures, neuropathy, cerebrovascular disease, chorea, headache
 9. Renal: Glomerulonephritis, tubulointerstitial nephritis, proteinuria, uremia, hypertension, renal insufficiency
 10. Hematologic: Thrombocytopenia, leukopenia, lymphopenia, hemolytic anemia
- C. Rheumatologic Markers in SLE
1. ANA
 - a. First screening test for SLE
 - b. High sensitivity (greater than 95%): ANA-negative SLE is rare.
 - c. Low specificity: ANA is often positive in patients with other autoimmune diseases (e.g., scleroderma, rheumatoid arthritis, JIA, Sjögren syndrome, polymyositis), autoimmune hepatitis, certain infections (Epstein-Barr virus, HIV, hepatitis C), and certain malignancies.
 - d. About 30% of healthy individuals have an ANA titer of 1:40 (as measured by immunofluorescence); as a result, a titer of 1:80 or greater is usually considered significant and warrants further investigation.
 2. Several other laboratory markers are used in conjunction with the clinical presentation to establish the diagnosis of SLE (e.g., anti-double-stranded DNA [anti-dsDNA] antibodies, anti-Smith antibodies, antiphospholipid antibodies, complement C3, complement C4)
 3. Follow-up monitoring of laboratory markers is usually not helpful (but is sometimes done clinically) because laboratory markers do not necessarily correlate with disease activity.
- D. Classification (Table 7)
1. SLICC (Systemic Lupus International Collaborating Clinics) classification (2012): Classifies a patient as having SLE if four of the clinical and immunologic criteria are present, including at least one clinical criterion and one immunologic criterion (do not need to be present concurrently) or if patient has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies. EULAR/ACR (European League Against Rheumatism/American College of Rheumatology) classification (2019): Requires presence of ANA at a titer of 1:80 or higher as the “entry criterion.” If ANA is less than 1:80, should not be classified as SLE. If elevated ANA titer is present, additive criteria from Table 7 should be applied as follows:
 - a. SLE classification requires at least one clinical criterion AND at least 10 points,
 - b. Within each clinical domain (e.g., constitutional, hematologic), only the highest weighted criterion is counted toward the total score.
- E. Cause: Unknown but thought to be multifactorial secondary to genetic, immunologic, and environmental factors
- F. General Pathogenesis:
1. Phagocytosis and clearing of immune complexes, apoptotic cells, and necrotic cell-derived material are defective in SLE. The mediators of SLE are autoantibodies and immune complexes that form with antigens.
 2. B cells that make autoantibodies are more persistently activated and driven to maturation.

3. Some antibody/antigen complexes activate the innate immune system by toll-like receptors. Thus, dendritic cells are activated and release type 1 interferons and TNF α . T cells release interferon γ , IL-6, and IL-10. These cytokine patterns favor continued autoantibody formation.
- G. Pharmacologic Therapy: Should be tailored according to disease activity and severity, pattern of organ involvement, and number of flares
1. Azathioprine (Imuran)
 - a. Use: Used for systemic features of lupus and maintenance therapy for LN; helps decrease steroid use; methyltransferase (TPMT) and nucleotide diphosphatase (NIDT 15) can be considered to identify individuals at high risk of myelosuppression
 - b. Dose: 1–3 mg/kg/day once daily
 - c. Adverse effects: Thrombocytopenia, leukopenia, GI intolerance, elevated LFTs
 2. Belimumab (Benlysta)
 - a. Monoclonal antibody that inhibits B-lymphocyte stimulator (cytokine that promotes B-cell activation and differentiation), FDA approved for age 5 years and older to treat clinically active SLE
 - b. Dose: 10 mg/kg/dose intravenously every 2 weeks for three doses, then 10 mg/kg/dose every 4 weeks. A subcutaneous formulation is available for adults 18 years and older.
 - c. Adverse effects: Infection, infusion reactions, psychiatric disturbances. Not recommended in patients with neuropsychiatric SLE features
 3. Corticosteroids
 - a. Commonly used in SLE, particularly to help control flares and induce remission
 - b. There are no agreed-on dosing regimens for corticosteroids, and practices vary between institutions. In general, high doses are used during flares and then tapered over several weeks/months, depending on response. Although patients should ideally be off steroids, many patients need these agents to achieve disease control.
 - c. For example, in patients with LN, induction therapy usually includes pulse dosing of high doses of methylprednisolone about 30 mg/kg intravenously daily (or 0.6–1 g/m²/day, max 1 g) for 3 days, followed by high-dose oral prednisone 1–2 mg/kg/day (max 60–80 mg/day), weaned over 6–8 weeks (depending on response) to about 0.5 mg/kg/day. Maintenance therapy usually consists of prednisone 0.05–0.2 mg/kg/day (or 5–10 mg/day); some clinicians use alternate-day dosing such as prednisone 10 mg every other day to minimize adverse effects.
 - d. Topical corticosteroids are used for cutaneous lupus.
 4. Cyclophosphamide (Cytosan)
 - a. Mechanism of action: Alkylating agent, suppresses DNA synthesis, suppresses helper T cells and B cells
 - b. Use: LN (prevents progression of renal disease, decreases proteinuria), severe SLE
 - c. Dose: Different dosing protocols exist.
 - i. High dose 500–1000 mg/m² (max 1500 mg) intravenously monthly $\times$ 6 doses
 - ii. Low dose: 500 mg intravenously every 2 weeks for six doses
 - d. Adverse effects: Alopecia, amenorrhea, gonadal suppression, infertility, bone marrow suppression, hemorrhagic cystitis
 5. Cyclosporine (Sandimmune, Neoral, Gengraf)
 - a. Use: Severe SLE; mainly used in LN
 - b. Dose: 1.5–5 mg/kg/day; target trough about 100 ng/mL
 - c. For adverse effects as of July 2021, refer to the section on Solid Organ Transplantation.
 6. Hydroxychloroquine (Plaquenil)
 - a. Mechanism of action: Many immunomodulatory effects – Inhibition of antigen processing and presentation, inhibition of cytokine release, binding to anti-dsDNA antibodies, and so forth

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- b. Use: Decreases flares; has cholesterol-lowering and antithrombotic effect; usually recommended to all patients with SLE regardless of disease severity
 - c. Slow onset of action
 - d. Dose: 3–5 mg/kg/day (max adult dose 400 mg/day)
 - e. Adverse effects: Retinal toxicity (dose-dependent) requiring regular eye examinations, nausea, diarrhea, skin pigmentation
 7. Methotrexate (Trexall)
 - a. Use: Mainly used in patients with skin or joint manifestations. Few pediatric studies
 - b. Dosing regimen: 10–15 mg/m²/week with 1 mg/day of folic acid
 - c. Adverse effects: Diarrhea, stomatitis, hepatotoxicity, renal toxicity, rash, bone marrow suppression, immunosuppression
 8. Mycophenolate mofetil (CellCept), mycophenolate sodium (Myfortic)
 - a. Use: Moderate to severe SLE, induction and maintenance of LN
 - b. Dose: 600–1200 mg/m²/day (max 3 g/day) orally in two divided doses
 - c. Adverse effects: GI intolerance, cytopenia, risk of infection
 9. NSAIDs: An option for mild disease but usually avoided because most pediatric patients have concomitant chronic kidney disease
 10. Rituximab (Rituxan)
 - a. For mechanism of action, refer to the section on Solid Organ Transplantation.
 - b. Use (off-label): Severe/refractory SLE, usually in patients with renal manifestations. Although observational studies (including pediatric studies) showed benefit, two randomized studies (of adults) did not.
 - c. Dose: 375 mg/m² intravenously weekly for two to four doses (e.g., variable regimens have been used such as extended frequencies, higher/lower doses, additional doses)
 - d. For adverse effects, refer to the section on Solid Organ Transplantation.
 11. Tacrolimus (Prograf)
 - a. For mechanism of action, refer to the section on Solid Organ Transplantation.
 - b. Use: Severe SLE; mainly used in LN
 - c. Dose: 1–3 mg (0.04–0.075 mg/kg) orally once daily, trough about 5 ng/mL
 - d. For adverse effects, see the Solid Organ Transplantation section.
 12. Other potential therapies (use in special circumstances because limited data are available)
 - a. Abatacept (Orencia)
 - b. Belimumab (Benlysta)
 - c. Bortezomib (Velcade)
 - d. Etanercept (Enbrel)
 - e. Infliximab (Remicade)
 - f. Tocilizumab (Actemra)
 - g. Voclosporin (Lupkynis)
 - h. Anifrolumab (Saphnelo)
- H. Lupus Nephritis
1. Occurs in 50%–75% of all pediatric patients
 2. Pathogenesis: Immune complexes deposit in the mesangial or subendothelial aspect of the glomerular basement membrane, activate the complement system, and generate chemotactic factors that attract the infiltration of leukocytes and mononuclear cells. These cells phagocytose immune complexes and release mediators that perpetuate glomerular inflammation.
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3. Diagnosis:
 - a. Proteinuria (urine protein/creatinine ratio greater than 0.5)
 - b. Renal biopsy
 - i. Class I – Minimal mesangial immune deposits
 - ii. Class II – Mesangial proliferative LN
 - iii. Class III – Focal LN (less than 50% of glomeruli), active versus chronic lesions
 - iv. Class IV (most common) – Focal LN (50% or more of glomeruli), active versus chronic lesions
 - v. Class V – Membranous LN; may have concomitantly with class III or IV
 - vi. Class VI – Advanced sclerosing LN (90% glomeruli or greater)
4. Treatment
 - a. Consists of two stages: Induction (aimed at inducing remission of disease flare) and maintenance (avoiding relapse)
 - b. See Table 8.

Table 7. 2019 EULAR/ACR Criteria vs. 2012 SLICC Classification of SLE

EULAR/ACR Classification (2019)	SLICC Classification (2012)
Clinical Criteria	
Constitutional: • Fever (2 points)	(Sub)acute cutaneous lupus (including malar rash and photosensitivity rash)
Hematologic: • Leukopenia (3 points) • Thrombocytopenia (4 points) • Autoimmune hemolysis (4 points)	
Neuropsychiatric: • Delirium (2 points) • Psychosis (3 points) • Seizure (5 points)	Chronic cutaneous lupus (including discoid rash)
Mucocutaneous: • Non-scarring alopecia (2 points) • Oral ulcers (2 points) • Subacute cutaneous OR discoid lupus (4 points) • Acute cutaneous lupus (6 points)	Oral or nasal ulcers
	Nonscarring alopecia
Serosal: • Pleural or pericardial effusion (5 points) • Acute pericarditis (6 points)	Synovitis, morning stiffness
Musculoskeletal: • Joint involvement (6 points)	Pleuritis, pericarditis
Renal: • Proteinuria > 0.5 g/24 hr (4 points) • Renal biopsy class II or V lupus nephritis (8 points) • Renal biopsy class III or IV lupus nephritis (10 points)	Renal disease (urine protein/creatinine ratio (or 24-hr urine protein) of 500 mg/24 hr, or RBC casts)
	Neurologic disease (seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state)

Table 7. 1997 ACR Criteria vs. 2012 SLICC Classification of SLE (*continued*)

EULAR/ACR Classification (2019)	SLICC Classification (2012)
Immunologic Criteria	
Antiphospholipid antibodies: • Anti-cardiolipin antibodies OR • Anti- β -2 glycoprotein 1 antibodies OR • Lupus anticoagulant (2 points)	Hemolytic anemia
	Leukopenia ($< 4000/\text{mm}^3$), or lymphopenia ($< 1000/\text{mm}^3$)
	Thrombocytopenia ($< 100,000/\text{mm}^3$)
Complement proteins: • Low C3 OR low C4 (3 points) • Low C3 AND low C4 (4 points)	ANA concentration
SLE-specific antibodies: • Anti-dsDNA antibodies OR • Anti-Smith antibodies	Anti-dsDNA antibody level
	Anti-Sm antibody
	Antiphospholipid antibody
	Low complement (C3, C4, CH50)
	Direct Coombs test without hemolytic anemia

EULAR/ACR = European League Against Rheumatism/American College of Rheumatology; SLE = systemic lupus erythematosus; SLICC = Systemic Lupus International Collaborating Clinics.

Table 8. Treatment of Lupus Nephritis

Lupus Nephritis	Treatment
Class I/II	No immunosuppressants required; ACEI or ARBs for proteinuria
Class III/IV	Induction: MMF or CYC <i>plus</i> Corticosteroids Maintenance: MMF or AZA <i>plus</i> Corticosteroids
Class V	MMF <i>plus</i> corticosteroids
Refractory disease (no response after 6 mo of treatment)	Change from CYC to MMF or from MMF to CYC or change to rituximab or change to calcineurin inhibitor <i>plus</i> Corticosteroids

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AZA = azathioprine;
CYC = cyclophosphamide; MMF = mycophenolate mofetil.

5. Adjunctive therapy for the following conditions may be needed:
 - a. Proteinuria
 - b. Hypertension
 - c. Fluid overload
 - d. Hypercoagulability
 - e. Lipid control
 - f. Vitamin D deficiency

I. Neonatal Lupus

1. Transplacental passage of maternal autoantibodies that can damage the fetal tissue.
2. Occurs in about 2% of children born to mothers with autoimmune disease, primarily SLE and Sjögren syndrome. Some women may have autoantibodies but no clinical disease. The risk increases to 15%–20% in women who have had a previous child with neonatal lupus.
3. Manifestations:
 - a. Cardiac manifestations – Usually 18–24 weeks' gestation. Heart block of varying degrees; complete heart block is the most serious complication
 - b. Rash – Observed about 6 weeks after birth, worsened by sunlight. Usually resolves within 6 months
 - c. Others – Elevated LFTs, cytopenia. Children with a history of neonatal lupus are at an increased risk of autoimmune disease, but not specifically SLE.
4. Prevention: Hydroxychloroquine may decrease the risk of cardiac abnormalities and is recommended to all pregnant women who had a child with cardiac neonatal lupus.
5. Treatment: Cutaneous, hematologic, and hepatobiliary; manifestations resolve spontaneously. Depending on the severity of cardiac manifestations, some patients may need a pacemaker.

J. Drug-Induced Lupus

1. Lupus-like syndrome temporally related to a specific drug exposure
2. Pathogenesis: Not clearly established, but several hypotheses exist:
 - a. Altered T-cell function because of DNA hypomethylation
 - b. Drugs acting as haptens or agonists for drug-specific T cells
 - c. Cytotoxic drug metabolites causing pathology
3. Several different drugs have been implicated, and risk varies between individual drugs.
 - a. Drugs identified to definitively cause drug-induced lupus include procainamide, hydralazine, minocycline, isoniazid, quinidine, and carbamazepine. Many other drugs have possible association.
 - b. Risk of drug-induced lupus highest with procainamide (15%–20%) and hydralazine (5%–8%)
4. How to distinguish drug-induced lupus from systemic lupus
 - a. Patient with a history of chronic exposure (months to years) to a drug associated with drug-induced lupus
 - b. Usually presents as “mild” SLE. Arthralgia, myalgia, fever, and serositis common. Cutaneous involvement common with TNF inhibitors. Renal and neurologic involvement uncommon
 - c. Laboratory tests are commonly (more than 90%) positive for ANA and antihistone antibodies. In general, laboratory tests are negative for other antibodies.
5. Management: Discontinue causative agent, use NSAIDs for symptomatic relief; clinical/serological changes will resolve over time.

Patient Cases

Questions 13 and 14 pertain to the following case.

An 11-year-old girl (weight 41 kg) presents to the pediatric rheumatology clinic for a photosensitive rash on her right midcheek extending to the infraorbital area and the nose. The rash was biopsied and identified as discoid lupus erythematosus. Subsequent laboratory studies showed an ANA titer of 1:320 and an anti-DNA antibody titer of 1:80 but no proteinuria and a normal SCr concentration. The patient has no significant medical history, and she is not taking any medications. Except for the cheek rash, her physical examination is largely unremarkable.

13. Which treatment is most appropriate for the patient at this time?
- A. Do not recommend any pharmacologic therapy right now, and advise the patient to wear sunscreen when going outside.
 - B. Recommend triamcinolone 0.1% cream twice daily, and advise the patient to wear sunscreen when going outside.
 - C. Recommend prednisone 40 mg orally once daily for 1 week, and advise the patient to wear sunscreen when going outside.
 - D. Recommend naproxen 250 mg orally twice daily, and advise the patient to wear sunscreen when going outside.
14. Which long-term treatment plan is most appropriate to recommend for this patient?
- A. Do not initiate any pharmacologic therapy, but continue to monitor lupus laboratory markers and renal function every 6 months.
 - B. Initiate prednisone 5 mg orally once daily, and monitor lupus laboratory markers and renal function every 6 months.
 - C. Initiate naproxen 250 mg orally twice daily, and monitor lupus laboratory markers and renal function every 6 months.
 - D. Initiate hydroxychloroquine 200 mg orally once daily, and monitor lupus laboratory markers and renal function every 6 months.
15. A 17-year-old female adolescent (weight 57 kg, body surface area 1.65 m²) received a diagnosis of class IV LN about 1 year ago. She was treated but was then lost to follow-up about 9 months ago. The patient states that she is taking mycophenolate mofetil 250 mg orally twice daily and hydroxychloroquine 200 mg orally once daily. The patient has knee and ankle pain, malar rash, gum bleeding, and mouth pain. Pertinent laboratory studies include the following: WBC 4×10^3 cells/mm³, ANA titer greater than 1:640, anti-DNA antibody titer greater than 1:640, SCr 1.8 mg/dL, and total protein in urine 3.5 g/24 hours. The patient is subsequently hospitalized for worsening of LN. Which regimen is best for treating her disease?
- A. Start methylprednisolone 1 g intravenously once daily for three doses; then change to prednisone 60 mg orally daily; increase mycophenolate mofetil to 1000 mg orally twice daily; continue hydroxychloroquine.
 - B. Start methylprednisolone 1 g intravenously once daily for three doses; increase mycophenolate mofetil to 1000 mg orally twice daily; continue hydroxychloroquine.
 - C. Start methylprednisolone 1 g intravenously once daily for three doses; then change to prednisone 60 mg orally once daily; continue mycophenolate mofetil 250 mg orally twice daily and hydroxychloroquine 200 mg orally once daily.
 - D. Start methylprednisolone 1 g intravenously once daily for three doses; then change to prednisone 60 mg orally once daily; continue mycophenolate mofetil 250 mg orally twice daily; hold hydroxychloroquine.

IX. HUMAN IMMUNODEFICIENCY VIRUS

- A. Epidemiology
 - 1. Globally, 38 million people were living with HIV in 2019.
 - 2. In the United States, approximately 1.2 million people have HIV. Around 34,800 were newly infected in 2019.
 - 3. The CDC estimates that 20% of new HIV infections occur in youths 24 years or younger and predominantly affect homosexual and bisexual males.
 - 4. About 10,000 individuals are living with perinatally acquired HIV.
- B. Transmission: Mainly through sexual intercourse and intravenous drug use. Less often transmitted perinatally
 - 1. Risk of transmission per act (sexual/intravenous drug use) for acquisition of HIV per 10,000 exposures to an infected source
 - a. Blood transfusion: 9250
 - b. Needle sharing: 63
 - c. Receptive anal intercourse: 138
 - d. Receptive vaginal intercourse: 8
 - e. Insertive anal intercourse: 11
 - f. Insertive vaginal intercourse: 4
 - g. Receptive oral intercourse: 1
 - h. Insertive oral intercourse: 0.5
 - 2. Perinatal transmission can occur:
 - a. Antepartum (in utero),
 - b. Intrapartum (most common), or
 - c. Postpartum (breastfeeding, pre-mastication).
 - d. Risk of transmission increases with the mother's viral load (1% if the mother's viral load is undetectable, around 20% if the viral load is greater than 30,000 copies/mL).
- C. Pathogenesis
 - 1. Acute infection (lasts about 3 months): HIV enters the host and infects dendritic cells, T cells, and macrophages. This leads to viremia and widespread seeding into lymphoid tissue. At this stage, patients have very high viral loads and are highly contagious.
 - 2. Clinical latency/chronic infection (lasts up to 15 years): Some immune containment of the virus through the host immune response and production of antibodies – Gradual loss of CD4 cells by productive infection or other mechanisms. Patients are usually asymptomatic in this phase.
 - 3. Clinical symptoms/AIDS (2 years or longer): Severe CD4 cell loss leading to opportunistic infections (OIs)
- D. HIV Life Cycle
 - 1. Viral envelope protein, glycoprotein 120, binds to the CD4 cell and coreceptor CCR5 (or CXCR4)
 - 2. Reverse transcription of the viral RNA genome by reverse transcriptase into dsDNA
 - 3. Integration of viral DNA into the cell's DNA
 - 4. Transcription and translation of the viral genome to produce viral proteins – Cleavage and assembly of viral proteins
 - 5. Release and then maturation of the virus through cleavage of immature polypeptides into functional polypeptides by protease enzyme

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- E. Laboratory Monitoring: CD4 count and viral load are the two main markers of disease progression and efficacy of antiretroviral therapy (ART).
1. CD4 count
 - a. Provides information on the overall immune function
 - b. In general, the higher the CD4 count, the better functioning of the immune system (no particular set goal).
 - c. Marker for initiation of antimicrobial prophylaxis against OIs (CD4 count less than 200 cells/mm³)
 - d. Usually measured every 3–4 months while on ART
 2. Viral load
 - a. Goal is to be undetectable (or less than 20 copies/mL).
 - b. Very high during acute infection (greater than 100,000 copies/mL)
 - c. Correlates with risk of transmission and risk of progression to AIDS
 - d. Usually measured every 3–4 months in patients on a stable ART regimen (more often if changing/modifying regimens)
 3. Resistance testing
 - a. General recommendations:
 - i. Genotypic testing is recommended before initiating ART.
 - ii. Need about 500 copies/mL or more to be performed
 - b. Genotype
 - i. Tests available to identify mutations in the reverse transcriptase and protease genes
 - ii. Can also check for integrase resistance but usually only done in treatment-experienced individuals
 - iii. Takes 1–2 weeks to receive results
 - c. Phenotype
 - i. Patient's virus is exposed to varying concentrations of each drug. The ability of the patient's virus to grow in the presence of the drugs is compared with the wild-type virus.
 - ii. Preferred for individuals with known or suspected complex drug-resistance mutation patterns
 - iii. Takes 2–3 weeks to receive results
 4. *HLA-B*5701* testing before abacavir initiation
 - a. Recommended to assess risk of hypersensitivity reaction
 - b. Symptoms of a hypersensitivity reaction may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, fatigue, or respiratory symptoms (sore throat, cough, or shortness of breath).
 - c. *HLA-B*5701*-positive patients should not receive abacavir, and a positive status should be recorded as an allergy.
 5. Routine monitoring
 - a. Physical examination, adherence assessment, CBC with differential, viral load, and chemistry panel are recommended every 3–4 months.
 - b. Urinalysis and lipid panel are recommended every 6–12 months.
 - c. Laboratory testing may be required more often if significant abnormalities are detected.
- F. Acute HIV Infection
1. Patients usually develop symptoms 2–4 weeks after exposure to HIV.
 2. Signs/symptoms (one or more of the following):
 - a. Fever, lymphadenopathy, rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leukopenia, thrombocytopenia, transaminase elevation
 - b. Some patients may be asymptomatic.
-

3. Diagnosis:
 - a. Detectable HIV RNA or p24 antigen in the setting of a negative or indeterminate HIV antibody test result
 - b. Antibody testing should be repeated 3–6 months later to document seroconversion.
 4. Treatment is recommended during acute infection.
- G. AIDS: Presence of AIDS depends on the CD4 count or the presence of an AIDS-defining illness.
1. Children younger than 1 year with a CD4 count less than 750 cells/mm³
 2. Children 1–5 years of age with a CD4 count less than 500 cells/mm³
 3. Children 6 years and older with a CD4 count less than 200 cells/mm³
 4. Examples of AIDS-defining illnesses (see complete list at <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5710a2.htm>)
 - a. Bacterial infections (multiple or recurrent)
 - b. Candidiasis of esophagus, bronchi, trachea, or lungs
 - c. CMV retinitis
 - d. Progressive multifocal leukoencephalopathy
 - e. PJP
 - f. Mycobacterial infections, etc.
- H. Preventive Strategies
1. HIV testing among adolescents
 2. Disclosure of HIV status to partners
 3. Male circumcision: Reduces a man's risk of acquiring HIV through heterosexual contact. However, it does not reduce the woman's risk of acquiring HIV and likely has only a small effect in men who have sex with men.
 4. Treatment of other sexually transmitted infections (STIs)
 5. Preexposure prophylaxis (PrEP) (last updated 2021)
 - a. Risk reduction is estimated to be 60%–80%.
 - b. PrEP has been poorly studied in adolescents.
 - c. The ability of minors to consent for themselves (i.e., without parental consent) to receive care for the prevention of HIV is less well established, and laws may vary across different states.
 - d. Patients who qualify for PrEP
 - i. Adults and adolescents (weight at least 35 kg) at substantial ongoing risk of HIV exposure and acquisition
 - ii. Those with behaviors considered a substantial HIV risk: HIV-positive sexual partner, recent bacterial STI, history of inconsistent or no condom use, sharing injection equipment, HIV-positive injecting partner
 - e. Before dispensing PrEP, the patient needs to have:
 - i. Confirmed negative HIV test
 - ii. No contraindications to the medication regimen
 - iii. No signs/symptoms of an acute HIV infection
 - iv. Creatinine clearance 30 mL/minute/1.73 m² or higher
 - f. Regimen:
 - i. Truvada (tenofovir disoproxil fumarate/emtricitabine) 300/200 mg 1 tablet orally once daily, OR
 - ii. Tenofovir alafenamide/emtricitabine (Descovy) 25/200 mg 1 tablet orally once daily (this option only for men and transgender women), OR
 - iii. Cabotegravir 600 mg intramuscularly (in the gluteal muscle) once, repeat in 4 weeks, then every 8 weeks thereafter

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- g. Monitoring: A follow-up is recommended every 3 months for Truvada and Descovy and every 2 months for cabotegravir, including:
 - i. HIV testing and bacterial STI screening
 - I. Non-occupational Postexposure Prophylaxis (nPEP)
 - 1. Rationale: To decrease the risk of HIV transmission after an unprotected exposure, most commonly sexual intercourse or intravenous drug use
 - 2. Risk reduction is estimated to be 80%.
 - 3. Exposure must have occurred within the past 72 hours to receive nPEP (nPEP not recommended if greater than 72 hours).
 - 4. Definition of a substantial exposure risk: Exposure of vagina, rectum, eye, mouth, or other mucous membrane; non-intact skin or percutaneous contact with blood, semen, vaginal secretions, rectal secretions, breast milk, or any body fluid that is visibly contaminated with blood
 - 5. Definition of negligible exposure risk: Exposure of vagina, rectum, eye, mouth, or other mucous membrane; intact or non-intact skin or percutaneous contact with urine, nasal secretions, saliva, sweat, or tears if not visibly contaminated with blood
 - a. If substantial exposure risk plus source was HIV positive – nPEP recommended
 - b. If substantial exposure risk plus HIV status of source is unknown – Case-by-case determination
 - c. If negligible exposure risk (regardless of HIV status of source) – nPEP not recommended
 - 6. Preferred treatment options
 - a. Children 4 weeks of age to younger than 2 years: Zidovudine plus lamivudine plus raltegravir or lopinavir/ritonavir
 - b. Children 2–12 years: Tenofovir disoproxil fumarate plus emtricitabine plus raltegravir
 - c. Children 13 years and older with normal renal function: Tenofovir disoproxil fumarate plus emtricitabine plus raltegravir or dolutegravir
 - d. Therapy duration is 28 days.
 - 7. Monitoring
 - a. Test for HIV antibodies at baseline, 4–6 weeks, and 3 months after exposure.
 - b. Testing for STIs, hepatitis B and C, and pregnancy should be offered.
 - c. Laboratory monitoring: CBC, SCr, LFTs
 - d. Counseling on signs and symptoms of an acute HIV infection
 - J. Perinatal Transmission (perinatal HIV transmission guidelines, last updated December 2021)
 - 1. General preventive strategies
 - a. Universal HIV testing
 - b. Effective HIV management for the mother throughout the pregnancy
 - c. Avoidance of breastfeeding and pre-mastication
 - d. Cesarean section if HIV viral load greater than 1000 copies/mL
 - e. Infant chemoprophylaxis after birth
 - 2. Treatment regimen recommendations for infant prophylaxis
 - a. Low risk (mother received ART during pregnancy and HIV RNA level less than 50 copies/mL within 4 weeks before delivery: Zidovudine prophylaxis for 4 weeks
 - b. Higher risk (mother did not receive ART during pregnancy, HIV RNA level greater than 50 copies/mL within 4 weeks of delivery or acute HIV infection during pregnancy) → presumptive HIV treatment: Zidovudine, lamivudine, and raltegravir OR zidovudine, lamivudine, and nevirapine for up to 6 weeks
-

3. HIV testing in exposed infants
 - a. DNA and RNA PCRs are the recommended assays. Standard antibody testing is not recommended because maternal HIV antibody crosses the placenta and will be detectable in all HIV-exposed infants up to age 18 months.
 - b. HIV virologic testing should be done
 - i. Within the first 14–21 days of life,
 - ii. At 1–2 months of age and
 - iii. At 4–6 months of age.
 - c. Clinicians also often test at birth. Sensitivity of DNA PCR is about 55% at birth and greater than 90% after 2 weeks.
 - d. Definitive exclusion of HIV infection is based on two or more negative virologic tests, with one obtained at age 1 month and older and one at age 4 months and older, or two negative HIV antibody tests from separate specimens obtained at age 6 months and older.
- K. Treatment in Children (pediatric HIV guidelines, last updated December 2021)
 1. General recommendations – ART is recommended to all HIV-positive patients regardless of CD4 count.
 2. Creating a regimen
 - a. In general, a basic regimen consists of three active drugs: In most cases, this means two nucleoside reverse transcriptase inhibitors (NRTIs) and one protease inhibitor (PI) *or* two NRTIs and one integrase strand transfer inhibitor (INSTI). Occasionally, two NRTIs and one nonnucleoside reverse transcriptase inhibitor are used, but this is considered second line. Of note, there are a few exceptions to this. In these exceptions, only two active drugs are needed to create an effective regimen; however, they have been largely studied in adults.
 - b. Table 9 summarizes the preferred NRTI combinations in children. In addition to two NRTIs, the patient will need either an INSTI or a PI – the specific recommendations vary by age (and sometimes weight). See table 7 in the pediatric HIV guidelines for additional information (<https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/regimens-recommended-initial-therapy-antiretroviral-naive-children?view=full>).
 - c. Table 10 describes each drug in detail. Table 10 intentionally excludes certain antiretroviral agents that are rarely used in clinical practice because of inferior potency, adverse effects, or both (e.g., atazanavir, darunavir, didanosine, efavirenz, enfurvitide, etravirine, fosamprenavir, indinavir, maraviroc, nelfinavir, rilpivirine, ritonavir, saquinavir, and tipranavir).
 3. Treatment of sexually mature adolescents (12 years and older and sexual maturity rating IV or V) and adults: Table 11 summarizes the preferred regimens (adult and adolescent HIV guidelines, last updated January 2022).

Table 9. Preferred NRTI Combinations in Children

Age	NRTI Combination
Birth – 5 yr	Zidovudine plus (lamivudine or emtricitabine)
≥ 1 mo	Abacavir plus (lamivudine or emtricitabine)
≥ 6 yr ^a	Tenofovir alafenamide and emtricitabine

^aAssumes weight ≥ 25 kg and sexual maturity rating [SMR] = 1–3.

NRTI = nucleoside reverse transcriptase inhibitor.

Table 10. Summary of Antiretroviral Drugs

Generic (Brand) Name	Minimum Age or Weight	Usual Dose	Formulation	Adverse Effects	Comments
NNRTIs					
Nevirapine (Viramune)	At birth	Give IR QD for 14 days (lead-in dosing because of autoinduction) and then increase to BID, or give IR QD for 14 days and then change to XR QD. Note that lead-in dosing may not be necessary for children < 2 yr IR formulation or suspension: 6 mg/kg/dose without lead-in dosing (gestational age $\geq$ 37 wk to < 1 mo) 200 mg/m ² /dose (1 mo – 7 yr); 120–150 mg/m ² /dose ($\geq$ 8 yr) XR formulation ($\geq$ 6 yr): 200 mg (BSA 0.58–0.83); 300 mg (BSA 0.84–1.16); 400 mg (BSA $\geq$ 1.17) Adolescent dose: 200 mg IR BID or 400 mg XR QD	Suspension (10 mg/mL); tab IR (200 mg), XR (100, 400 mg)	Rash (usually during first 6 wk of therapy), hepatitis (usually during first 12 wk of therapy), hypersensitivity reaction	
Integrase Inhibitors					
Bictegravir	$\geq$ 25 kg	1 tab PO QD	Only available in fixed-dose combination as part of Biktarvy	Diarrhea, nausea, headache	Additional adverse drug reactions present from other ARTs that are combined with bictegravir (Biktarvy)
Dolutegravir (Tivicay)	$\geq$ 3 kg	1. Dispersible tabs ($\geq$ 4 wk): 5 mg (3–5.9 kg); 15 mg (6–9.9 kg); 20 mg (10–14.9 kg); 25 mg (15–19.9 kg); 30 mg ($\geq$ 20 kg) 2. Film-coated tab: 40 mg (14–19.9 kg); 50 mg ($\geq$ 20 kg)	Film-coated tab (10, 25, 50 mg) Dispersible tablets for oral suspension (5 mg)	Insomnia, headache, neuropsychiatric symptoms	Separate from cation-containing medications, film-coated and dispersible tabs are not interchangeable
Elvitegravir	$\geq$ 25 kg	1 tab PO QD	Only available in fixed-dose combination as part of Stribild and Genvoya	Diarrhea	Additional adverse drug reactions present from other ARTs that are combined with elvitegravir (Stribild, Genvoya)

Table 10. Summary of Antiretroviral Drugs (*continued*)

Generic (Brand) Name	Minimum Age	Usual Dose	Formulation	Adverse Effects	Comments
Raltegravir (Isentress)	Birth	1. Film-coated tab (≥ 25 kg): 400 mg PO BID 2. Film-coated HD tab (≥ 40 kg) 1200 mg PO QD (treatment-naïve) 3. Chewable tab (≥ 11 kg) 75 mg (11–13 kg) 100 mg (14–19 kg) 150 mg (20–27 kg) 200 mg (28–39 kg) 300 mg (≥ 40 kg) Given BID 4. Oral suspension: Neonates ≥ 37 wk gestation (weighing ≥ 2 kg): Birth to 1 wk: QD 4 mg (2–2.9 kg) 5 mg (3–3.9 kg) 7 mg (4–4.9 kg) 1–4 wk: BID 8 mg (2–2.9 kg) 10 mg (3–3.9 kg) 15 mg (4–4.9 kg) (≥ 4 wk): 25 mg (3–3.9 kg) 30 mg (4–5.9 kg) 40 mg (6–7.9 kg) 60 mg (8–10.9 kg) 80 mg (11–13.9 kg) 100 mg (14–19.9 kg) Given BID	Film-coated tab (400 mg); High-dose film-coated HD tab (600 mg); chewable tab (100, 25 mg); Granules for oral suspension (100 mg)	Rash, nausea, diarrhea, headache, insomnia, fever, CK elevations	Different formulations are not interchangeable (chewable tab and suspension are more bioavailable than film-coated tab) Avoid coadministration with Al- or Mg-containing antacids
NRTIs					
Abacavir (Ziagen)	≥ 3 mo	Solution (≥ 3 mo) 8 mg/kg/dose BID Tab (≥ 14 kg): 150 mg BID (14–20 kg) 150 mg in AM and 300 mg in PM (20 to ≤ 25 kg) 300 mg BID or 600 mg QD (≥ 25 kg)	Solution (20 mg/mL); tab (300 mg)	Nausea, vomiting, fever, headache, diarrhea, rash, hypersensitivity reaction (fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, and respiratory symptoms)	Test <i>HLA-B*5701</i> before initiation to predict risk of hypersensitivity reaction → do not give if test positive

Table 10. Summary of Antiretroviral Drugs (*continued*)

Generic (Brand) Name	Minimum Age	Usual Dose	Formulation	Adverse Effects	Comments
Emtricitabine (Emtriva)	At birth	1. Solution: 3 mg/kg QD (0–2 mo); 6 mg/kg (max 240 mg) QD (3 mo – 17 yr); 2. Cap: 200 mg QD (> 33 kg);	Solution (10 mg/mL); cap (200 mg) Multiple in multiple other coformulations (see Combination Products section)	Hyperpigmentation on palms/soles	Screen for HBV before start
Lamivudine (Epivir)	At birth	1. Solution: 2 mg/kg BID (< 4 wk); 4 mg/kg BID (4 wk to 2 mo); 5 mg/kg (max 150 mg) BID (≥ 3 mo); 10 mg/kg (max 300 mg) QD (≥ 3 yr); 2. Tab (≥ 14 kg): 75 mg BID (14 to ≤ 20 kg); 75 mg qAM and 150 mg qPM (20 to ≤ 24 kg); 150 mg BID (≥ 25 kg))	Solution: 10 mg/mL (Epivir), 5 mg/mL (Epivir HBV); tab (100, 150, 300 mg)	Headache, nausea	Screen for HBV before start
Tenofovir disoproxil fumarate (Viread)	≥ 2 yr	1. Oral powder: 8 mg/kg/dose QD (2–11 yr) 2. Tab (≥ 12 yr and weight ≥ 17 kg): 150 mg QD (17–21 kg); 200 mg QD (22–27 kg); 250 mg QD (28–34 kg); 300 mg QD (≥ 35 kg)	Oral powder (40 mg/1 g oral powder = 1 scoop) Tab (150, 200, 250, 300 mg)	Nausea, diarrhea, headache, decreased renal function, Fanconi syndrome, decreased bone mineral density	
Tenofovir alafenamide (TAF)	≥ 25 kg (weight cutoff may be higher depending on co-formulation)	1 tab QD	Tab (25 mg) [Note: 25-mg tabs are FDA approved for HepB only. Only available in fixed-dose combination for HIV treatment]	Nausea, diarrhea, headache, less renal and bone mineral toxicity than tenofovir disoproxil fumarate	TAF-containing formulations are not recommended in CrCl < 30 mL/min

Table 10. Summary of Antiretroviral Drugs (*continued*)

Generic (Brand) Name	Minimum Age	Usual Dose	Formulation	Adverse Effects	Comments
Zidovudine (Retrovir)	At birth	1. Prevention: ≥ 35 wk gestation at birth: 4 mg/kg PO q12hr; 30–35 wk gestation at birth: 2 mg/kg PO q12hr, advanced to 3 mg/kg PO q12hr at age 14 days; < 30 wk gestation at birth: 2 mg/kg PO q12hr; 2. Treatment: 4 mg/kg/dose BID (birth to 4 wk); 180–240 mg/m ² BID (4 wk – 17 yr); 300 mg BID (≥ 30 kg)	IV (10 mg/mL); syrup (10 mg/mL); tab (300 mg); cap (100 mg)	Bone marrow suppression, anemia, neutropenia, nausea, vomiting, headache, lactic acidosis, hepatomegaly, insulin resistance, lipoatrophy, myopathy	For infants unable to take zidovudine by mouth, IV dose is 75% of oral dose with same dosing interval
Protease Inhibitors					
Lopinavir/ritonavir (LPV/r) (Kaletra)	≥ 14 days (and postmenstrual age > 42 wk)	300 mg/75 mg/m ² /dose BID (14 days – 12 mo) Treatment experienced: 300 mg/75 mg/m ² /dose BID (1–18 yr); Treatment naive: 230 mg/57.5 mg/m ² /dose BID (1–18 yr) Adults: 400/100 mg BID or 800/200 mg QD	Solution (LPV/r): 80 mg/20 mg/mL; film-coated tab (LPV/r): 100 mg/25 mg, 200 mg/50 mg	GI intolerance, nausea, vomiting, diarrhea, taste alteration, asthenia, hyperlipidemia, elevated LFTs, hyperglycemia, fat maldistribution, PR/QT-interval prolongation	Solution contains 42.4% alcohol by volume and 15.3% propylene glycol by weight/volume
Boosters					
Cobicistat (Tybost)	≥ 18 yr ≥ 25 kg for Genvoya	150 mg PO QD in combination with other ART	Tab (150 mg)	Increase in SCr by inhibition of tubular secretion (no harmful effect on renal function)	CYP3A inhibitor and several drug interactions; no activity against HIV itself; not interchangeable with RTV; do not combine with RTV

Al = aluminum; AM = morning; ART = antiretroviral therapy; BSA = body surface area; cap = capsule(s); HepB = hepatitis B vaccine; INSTI = integrase strand transfer inhibitor; IR = immediate release; LFT = liver function test; LPV/r = lopinavir/ritonavir; Mg = magnesium; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; PM = night; PPI = proton pump inhibitor; q = every; RTV = ritonavir; tab = tablet(s); UGT = uridine diphosphate glucuronyltransferase; VL = viral load; XR = extended release.

Table 11. Combination ART Regimens for Treatment-Naïve Adolescents and Adults

Preferred Regimens	
INSTI based	Bictegravir and tenofovir alafenamide/emtricitabine (Biktarvy)
	Dolutegravir and abacavir and lamivudine (Triumeq) if <i>HLA-B*57:01</i> negative and no chronic hepatitis B infection
	Dolutegravir plus (emtricitabine or lamivudine) + (tenofovir disoproxil fumarate or tenofovir alafenamide)
	^a Dolutegravir/lamivudine (Dovato) if no hepatitis B infection and HIV VL < 500,000 copies/mL

^aHIV genotypic resistance testing is needed before initiating this regimen.

4. Commonly used combination products (will need addition of another drug or drugs)
 - a. Cimduo, Temixys (lamivudine 300 mg/tenofovir disoproxil fumarate 300 mg) 1 tablet orally once daily
 - b. Descovy (emtricitabine 200 mg/tenofovir alafenamide 25 mg) 1 tablet orally once daily
 - c. Truvada (emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg) 1 tablet orally once daily
 - d. Truvada low-strength tablets (Emtricitabine 100 mg/tenofovir disoproxil fumarate 150 mg) 1 tab orally once daily (Emtricitabine 133 mg/tenofovir disoproxil fumarate 200 mg) 1 tab orally once daily (Emtricitabine 167 mg/tenofovir disoproxil fumarate 250 mg) 1 tab orally once daily
 - e. Trizivir (lamivudine 150 mg/abacavir 300 mg/zidovudine 300 mg) 1 tablet orally twice daily
5. Single-pill regimens (no additional drugs needed) for preferred regimens. A full list of single-pill regimens can be found in appendix A, table 2 of the pediatric ART guidelines: <https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/appendix-table-2-antiretroviral-fixed-dose-combination-tablets-minimum?view=full>.
 - a. Biktarvy (emtricitabine 200 mg/tenofovir alafenamide 25 mg/bictegravir 50 mg) 1 tablet orally once daily
 - b. Dovato (dolutegravir 50 mg/lamivudine 300 mg) 1 tablet orally once daily
 - c. Genvoya (emtricitabine 200 mg/tenofovir alafenamide 10 mg/elvitegravir 150 mg/cobicistat 150 mg) 1 tablet orally once daily
 - d. Triumeq (abacavir 600 mg/lamivudine 300 mg/dolutegravir 50 mg) 1 tablet orally once daily

Patient Case

Questions 16 and 17 pertain to the following case.

A 17-year-old male adolescent with no significant medical history has newly diagnosed HIV. His CD4 count is 525 cells/mm³ and viral load is 125,000 copies/mL. His genotype results reveal a pan-susceptible virus, and the patient wishes to start ART.

16. Which is the best first-line regimen to recommend for this patient?
 - A. Emtricitabine 200 mg and tenofovir alafenamide 25 mg 1 tablet orally once daily.
 - B. Emtricitabine 200 mg and tenofovir alafenamide 25 mg and bictegravir 50 mg 1 tablet orally once daily.
 - C. Emtricitabine 200 mg and cobicistat 150 mg 1 tablet orally once daily.
 - D. Emtricitabine 200 mg and zidovudine 300 mg and lamivudine 300 mg 1 tablet orally once daily.

Patient Case (continued)

17. Six months after the HIV diagnosis, the patient returns for a follow-up, accompanied by his new male partner. The partner is aware of the patient's HIV status and wishes to take medications to prevent HIV transmission. Assuming that the new partner is HIV negative, which regimen is best to recommend for HIV prevention?
- A. Administer emtricitabine 200 mg/tenofovir disoproxil fumarate 300 mg 1 tablet orally once daily.
 - B. Administer abacavir 600 mg and lamivudine 300 mg and dolutegravir 50 mg 1 tablet orally once daily
 - C. Administer emtricitabine 200 mg and lamivudine 300 mg 1 tablet orally once daily
 - D. Do not recommend antiretroviral prophylaxis to the patient's partner.

L. Immune Reconstitution Inflammatory Syndrome (IRIS)

1. Definition: Reconstitution of the immune system produces a disproportionate inflammatory response to antigens, which results in apparent clinical worsening of an existing OI or appearance of a new OI.
2. Two main types
 - a. "Unmasking" IRIS: There is an underlying subclinical, previously unrecognized infection, which flares after starting ART.
 - b. "Paradoxical" IRIS: Exacerbation of a past known, often-treated infection because of antigen-driven immune activation
3. Pathogenesis
 - a. Not clearly understood. After initiation of ART, viral load rapidly decreases and CD4 count rapidly increases, resulting in an increased ability to mount inflammatory responses.
 - b. Increased T-cell activation from antigenic exposure, increased production of proinflammatory chemokines/cytokines
 - c. Median time of onset is about 6 weeks to 3 months but can be longer.
 - d. Usually described in association with mycobacterial, fungal, and viral infections
4. Epidemiology: Incidence 10%–20% in resource-limited settings; 6%–7% in Western countries
5. Risk factors
 - a. Presence of active/subclinical infection
 - b. Low CD4 count (less than 100 cells/mm³)
 - c. Short interval (i.e., within 30 days) between initiation of ART and treatment of OI
 - d. Degree of viral load decline
6. Clinical manifestations: Depend on the type of infection present
 - a. Tuberculosis (most common): Lymphadenitis, pulmonary infiltrates, pleural effusions, meningitis, peritoneal and pericardial disease
 - b. Varicella zoster: Zoster flare
 - c. *Mycobacterium avium* complex (MAC): Lymphadenitis, pulmonary infiltrates, peritonitis, osteomyelitis, cutaneous abscesses
 - d. Herpes simplex: Presence of lesions
7. Treatment (Note: According to case series/reports because no randomized studies exist)
 - a. Mild disease: Observation with possible addition of NSAIDs for symptomatic relief
 - b. Severe disease: Corticosteroids such as prednisone 1–2 mg/kg for 1–2 weeks; then taper
 - c. ART usually need not be discontinued but can be considered in patients with severe clinical manifestations.
8. Prevention
 - a. Initiation of ART at higher CD4 counts: Already being done in Western countries
 - b. ART delay in patients with a new OI: Guidelines make no recommendation but instead recommend weighing risk-benefit and individualizing therapy.

M. OIs Associated with HIV Infection (pediatric OI guidelines, last updated November 2021)

1. In general, patients with HIV are at risk of several OIs; however, because of early detection and ART introduction, the incidence is relatively low in Western countries (incidence rate 1 or 2 per 100 person-years).
2. The most common OIs include bacterial infections, candidiasis, tinea, and varicella.
3. The risk of OIs increases as the CD4 count decreases. It is especially high once the CD4% is less than 15% (or less than 200 cells/mm³).
4. Prevention
 - a. Up-to-date immunizations
 - b. ART – Can lead to improvement in certain OIs for which no treatments exist (i.e., progressive focal leukoencephalopathy, cryptosporidium)
 - c. Primary prophylaxis (Table 12)
 - i. Initiation of antimicrobial prophylaxis to individuals at risk before development of an infection
 - ii. Currently indicated for MAC, PJP, toxoplasmosis, and tuberculosis
 - iii. Usually depends on the CD4% (or CD4 count). Exception: PJP prophylaxis recommended for all infants younger than 1 year, regardless of CD4%.
 - d. Secondary prophylaxis (see Table 12)
 - i. Initiation of antimicrobial prophylaxis after treatment for an infection to prevent recurrence
 - ii. Recommended for most infections
 - iii. Discontinuation usually depends on clinical status, infection resolution, and CD4% (or CD4 count).
5. Treatment
 - a. In general, treatment of OIs is the same as treatment in HIV-negative children. However, drug-drug interactions with ART can add another layer of complexity to OI management.
 - b. Full OI treatment guidelines in pediatric HIV are available at <https://aidsinfo.nih.gov/guidelines/html/5/pediatric-opportunistic-infection/0>.

Table 12. Select Primary and Secondary Prophylactic Antimicrobial Regimens for Children with HIV Infection

Disease	Primary Prophylaxis		Secondary Prophylaxis	
	First-line Regimen	Comments	First-line Regimen	Comments
Cytomegalovirus	None		Valganciclovir (mg) = $7 \times \text{BSA} \times \text{CrCl}$ (up to max of 150 mL/min/1.73 m ²) PO QD (max 900 mg/day) or 15–18 mg/kg PO QD ^a	Discontinuation can be considered if patient completed > 6 mo of ART, and CD4 % $\geq$ 15% for > 6 mo (if < 6 yr) or CD4 count > 100 cells/mm ³ for > 6 mo (if $\geq$ 6 yr). If retinitis present, consultation with ophthalmologist is recommended

Table 12. Primary and Secondary Prophylactic Antimicrobial Regimens for Children with HIV Infection (*continued*)

Disease	Primary Prophylaxis		Secondary Prophylaxis	
<i>M. avium</i> complex (MAC)	<i>Preferred:</i> Azithromycin 20 mg/kg (max 1200 mg) PO qwk or clarithromycin 7.5 mg/kg (max 500 mg) PO BID	Indication: CD4 count < 750 cells/mm ³ if < 1 yr; < 500 cells/mm ³ if 12–23 mo; < 75 cells/mm ³ if 2–5 yr; < 50 cells/mm ³ if ≥ 6 yr Duration: On ART for ≥ 6 mo and CD4 > 200 cells/mm ³ for > 3 mo (2–5 yr); CD4 > 100 cells/mm ³ for > 3 mo (≥ 6 yr). Note: Do not discontinue in children < 2 yr	Clarithromycin 7.5 mg/kg (max 500 mg) PO BID + ethambutol 15–25 mg/kg (max 2.5 g) PO QD	Can be discontinued once patient has completed ≥ 6 mo of ART and completed ≥ 12 mo MAC therapy and is asymptomatic for signs and symptoms of MAC, and CD4 > 200 cells/mm ³ for ≥ 6 mo (2–5 yr) or CD4 > 100 cells/mm ³ for ≥ 6 mo (≥ 6 yr) (must fulfill all criteria earlier)
<i>Mycobacterium tuberculosis</i>	Isoniazid 10–15 mg/kg (max 300 mg) PO QD	Indication: Positive TST (≥ 5 mm) or IGRA, or close contact with an infectious TB case Duration: 9 mo	None	
<i>P. jiroveci</i> pneumonia	<i>Preferred:</i> TMP 5–10 mg/kg (max 320 mg) with SMX 25–50 mg/kg (max 1600 mg) PO QD or three times weekly, or Dapsone 2 mg/kg (max 100 mg) PO QD or 4 mg/kg (max 200 mg) PO qwk or atovaquone 30–40 mg/kg (1–3 mo and 24 mo – 12 yr); 45 mg/kg (47–24 mo); 1500 mg (≥ 13 yr) given PO QD, or pentamidine 300 mg inhaled once monthly given with a Respigard II nebulizer	Indication: Infants 4–6 wk to 12 mo regardless of CD4%; CD4 < 500 cells/mm ³ (or < 15%) if 1–5 yr; CD4 < 200 cells/mm ³ (or < 15%) if ≥ 6 yr Duration: ART for ≥ 6 mo and CD4 ≥ 500 cells/mm ³ (or ≥ 15%) for > 3 mo if 1–5 yr, or CD4 count ≥ 200 cells/mm ³ (or ≥ 15%) for > 3 mo if ≥ 6 yr Do not discontinue in children < 1 yr	Same as primary prophylaxis	Same as primary prophylaxis

Table 12. Primary and Secondary Prophylactic Antimicrobial Regimens for Children with HIV Infection (*continued*)

Disease	Primary Prophylaxis		Secondary Prophylaxis	
Toxoplasmosis	<i>Preferred:</i> TMP/SMX 150/750 mg/m ² PO QD, or Dapsone 2 mg/kg (max 25 mg) PO QD <i>plus</i> pyrimethamine 1 mg/kg (max 25 mg) PO QD <i>plus</i> leucovorin 5 mg PO q3days	IgG antibody positive and CD4 < 15% (< 6 yr) or < 100 cells/mm ³ (≥ 6 yr) Duration: After ≥ 6 mo of ART and CD4 ≥ 15% (1–5 yr) or CD4 > 200 cells/mm ³ (≥ 6 yr) for > 3 mo. Note: Do not discontinue in children < 1 yr	Sulfadiazine 42.5–60 mg/kg/dose PO BID (max 2–4 g/day) + pyrimethamine 1 mg/kg (max 25 mg) PO QD + leucovorin 5 mg PO QD	Discontinuation recommended if patient completed ≥ 6 mo of ART and asymptomatic for toxoplasmic encephalitis and CD4 ≥ 15% for > 6 mo (1–5 yr) or CD4 > 200 cells/mm ³ for > 6 mo (≥ 6 yr) (must fulfill all criteria earlier)
Varicella zoster virus	<i>Preexposure:</i> Vaccination <i>Postexposure:</i> VariZIG 125 IU/10 kg IM (max 625 IU), within first 10 days of exposure	<i>Preexposure:</i> Because live attenuated vaccine, can be given to children with CD4% ≥ 15 (or ≥ 200 cells/mm ³ if > 8 yr) <i>Postexposure:</i> Indicated for unimmunized children with exposure to a contact with varicella or zoster Expert opinion recommends VariZIG in children with CD4 < 200 cells/mm ³ (or < 14%). If VariZIG not given, consider acyclovir 20 mg/kg (max 800 mg) QID for 7 days upon appearance of rash	None	

^aDosing information largely extrapolated from solid organ transplant recipients.

IGRA = interferon release assay; QID = four times daily; TB = tuberculosis; TMP/SMX = trimethoprim/sulfamethoxazole; TST = tuberculin skin test; VariZIG = varicella zoster immunoglobulin.

Patient Case

18. Which patient with HIV-positive infection would most likely require prophylaxis against PJP?

- A. 4-year-old girl with a CD4 of 24%.
- B. 16-year-old male adolescent with a CD4 of 490 cells/mm³.
- C. 8-year-old girl with a CD4 count of 320 cells/mm³.
- D. 3-month-old boy with a CD4 of 35%.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: C

Answer C is correct because triamcinolone is a medium-potency steroid and is more potent than the hydrocortisone therapies the patient was previously receiving. Answer A is incorrect because the patient's hydrocortisone therapy has already failed, and the patient would likely not improve with the administration of hydrocortisone at a decreased potency. Answer B is incorrect because clobetasol is a very high-potency steroid, and use on the face is usually avoided because of the risk of skin atrophy. Answer D is incorrect because crisaborole is FDA approved for children 2 years or older.

2. Answer: C

Answer C is correct because topical steroids are associated with skin atrophy, especially when used on the face and intertriginous areas. Answers A, B, and D are incorrect because topical steroids are not associated with the adverse effects listed within those options.

3. Answer: D

Answer D is correct because the patient's physical examination reveals that she has arthritis in only one joint, for which intra-articular steroid injections would be appropriate. Systemic therapy with steroids (Answer A) or anakinra (Answer C) would not be necessary. Moreover, increasing the methotrexate dose (Answer B) is incorrect because it is above the maximum recommended dose of 25 mg/day.

4. Answer: D

Answer D is correct because the patient is having an acute flare and will need to start systemic steroids for acute control of her symptoms in addition to restarting methotrexate. Furthermore, changing to the subcutaneous route may be beneficial in this patient because of the GI adverse effects that occur with the oral formulation. Answer A is not the best option because the patient has been having adverse effects with oral methotrexate. Answer B is not the best option; reinitiating methotrexate alone would not control her symptoms acutely because methotrexate takes about 6 weeks for full effect. Similarly, Answer C is incorrect because the adalimumab dose is high for weekly dosing; also, onset is delayed by 2–4 weeks and is unlikely to help because of the severity of her symptoms.

5. Answer: D

Answer D is correct because the patient is immunocompromised and needs to avoid all live vaccines, including rotavirus. Vaccines listed as other options in Answers A–C (influenza, pneumococcal, and DTaP) may have questionable efficacy; however, they are inactivated vaccines and will not cause disease.

6. Answer: A

Live vaccines should not be administered to patients receiving biologic agents such as TNF inhibitors, making Answer A correct and Answers B–D incorrect.

7. Answer: A

Answer A is correct because the recommended epinephrine dose is 0.01 mg/kg (0.2 mg on the basis of weight 20 kg), and 1:1000 (i.e., 1 mg/mL) is the recommended concentration. Answer B is incorrect because the dose calculation did not include conversion from pounds to kilograms. Answer C is incorrect because a 1:10,000 concentration contains 0.1 mg/mL; thus, a dose of 0.2 mL would provide only 0.02 mg. Answer D is incorrect because an intravenous infusion is recommended only in refractory anaphylaxis.

8. Answer: B

Answer B is correct because the patient missed several days of therapy and has likely lost tolerance to penicillin. As a result, he would need to be readmitted for a second desensitization. Answers A and C are incorrect because the patient has a history of an anaphylactic reaction to penicillin (regardless of route of administration) and should not be rechallenged without desensitization. Answer D is incorrect because antihistamines do not prevent anaphylaxis.

9. Answer: C

Answer C is correct because a prescription for epinephrine is recommended to provide immediate treatment for anaphylaxis if it occurs. Answers A, B, and D are incorrect because they are considered adjuncts to epinephrine treatment.

10. Answer: A

Answer A is correct because avoidance is currently recommended as the best management strategy for severe

food allergies. Answer D is incorrect because an antihistamine is unlikely to prevent anaphylaxis. Answer C is incorrect because most patients with tree nut allergies do not outgrow them. Answer B is incorrect because small amounts can precipitate an allergic reaction. In addition, if immunotherapy (development of tolerance by introducing almonds in small amounts and gradually increasing to the serving size amount) is being considered, benefit-risk needs to be discussed with the parents and patient, and it should be initiated in a clinical setting.

11. Answer: B

Answer B is correct because benzathine penicillin G is effective as secondary prophylaxis, needs to be administered monthly, and would help with patient adherence. Answer A would not be the best choice because the patient was not adherent to oral penicillin in the past. Answer C is incorrect; erythromycin is not first-line therapy for secondary prevention because of its adverse effects and reports of microbial resistance. Answer D is incorrect because clindamycin is currently recommended for primary prevention only.

12. Answer: D

Answer D is correct because the patient has severe valvular disease and would need to continue secondary prophylaxis at least until she is 40 years of age. Shorter therapies are reserved for patients with fewer cardiac complications, making Answers A–C incorrect.

13. Answer: B

Answer B is correct because the patient has cutaneous lupus only; she can be treated with topical corticosteroids in addition to avoiding unprotected sun exposure. Answer A is incorrect because pharmacologic therapy is available to help treat the patient's symptoms. Answer C is incorrect because systemic steroid therapy is likely not necessary for cutaneous involvement only. Answer D is incorrect because naproxen is used to manage arthritis symptoms, and the patient has no concerns other than rash.

14. Answer: D

Answer D is correct because hydroxychloroquine, which can decrease flares, is usually recommended for all patients with lupus. Answer B is incorrect; systemic corticosteroid therapy is not currently needed because

the patient's cutaneous symptoms will be treated with topical corticosteroids. Answer C is incorrect because naproxen is only likely to help with musculoskeletal symptoms. Answer A is incorrect because pharmacologic therapy is available to help treat the patient's symptoms.

15. Answer: A

Answer A is correct because it summarizes the recommended regimen for treating an acute flare of LN. Answer B is incorrect because it lacks the transition to oral prednisone once methylprednisolone therapy has been completed. Answers C and D are incorrect because the mycophenolate mofetil dose is too low. In addition, hydroxychloroquine is usually continued in all patients with lupus unless adverse effects related to the drug develop.

16. Answer: B

Answer B is correct because the combination regimen comes as 1 tablet (Biktarvy) taken orally once daily and is recommended as first line by the guidelines. Answer C is incorrect because it consists of one active antiretroviral (emtricitabine) and one booster (cobicistat), which is not recommended. Answer A is incorrect because it consists of only two NRTIs and is missing another drug. Answer D is incorrect because the regimen consists of three NRTIs, which is not recommended.

17. Answer: A

Answer A is correct because emtricitabine/tenofovir (Truvada) is currently the recommended prophylactic regimen for patients at high risk of acquiring HIV. Answers B and C are incorrect because they are considered full regimens for patients requiring treatment, not prophylaxis. Answer D is incorrect because this patient would be considered high risk; thus, he would qualify for HIV prevention.

18. Answer: D

Answer D is correct because all infants require PJP prophylaxis, regardless of their CD4 percentage or CD4 count. Answers A–C are incorrect because the patients in these cases all have a CD4 percentage greater than 15% or a CD4 count greater than 200 cells/mm³.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

Answer A is correct, according to the ACR guidelines, for the initial treatment of LN. Answer B is incorrect because glucocorticosteroids alone as immunosuppressive therapy are not recommended. Losartan itself would probably be appropriate for controlling proteinuria, but it is not part of the immunosuppressive therapy. Answer C is incorrect; mycophenolate mofetil and azathioprine are usually not used together because of their similar mechanism of action. Answer D is incorrect because including rituximab is usually recommended for refractory disease, not initial treatment.

2. Answer: C

Answer C is correct because benzathine penicillin G is the recommended secondary prevention prophylactic regimen for patients with a history of acute rheumatic fever. Answers A and B are incorrect because aspirin and steroids may be used in patients with symptoms of arthritis and carditis, respectively. Answer D is incorrect because amoxicillin at the listed dose is recommended for primary, not secondary, prevention of acute rheumatic fever.

3. Answer: B

Answer B is correct because desensitization is only a temporary state of tolerance that does not persist once chronic administration of a drug is halted. Answer A is incorrect because tolerance to a drug after desensitization usually does not persist lifelong. Answer C is incorrect because most desensitization procedures are successful, despite frequent (but mild) breakthrough reactions. Answer D is incorrect because desensitization can usually be completed within 1 day.

4. Answer: C

Answer C is correct; according to the ACIP guidelines, patients who tolerate egg in baked goods can receive the flu vaccine without additional precautions, whereas MMR can be given to all patients with egg allergy. Answers B and D are incorrect because patients can receive both vaccines as recommended. Answer A is incorrect because the ACIP guidelines recommend that a health care provider with expertise in allergy management should become involved if the patient develops a severe reaction to the influenza vaccine (e.g., hypotension, respiratory distress).

5. Answer: D

Answer D is correct because egg allergy testing in patients who have not had symptoms of food allergy is usually not recommended. Answers A and B are incorrect; allergy testing is not recommended in children who are at “high risk” of egg allergy because a sibling is allergic. In addition, these results are not useful for clinical correlation because many patients can have a “positive” reaction but not have the disease. Allergy testing is only useful in patients with a documented history of allergic reaction on ingestion of a potential food allergen. Answer C is incorrect because oral immunotherapy is reserved for patients with documented allergy as a way of inducing a state of tolerance to the allergen.

6. Answer: B

Answer B is correct because an HCT is the best long-term option for patients with SCID. Answer A is incorrect because gene therapy for X-linked disease, which is still being investigated, has had mixed results. Answer C is incorrect; IgG replacement is reasonable but not the best treatment option because patients require lifelong replacement. Finally, antimicrobial prophylaxis is usually indicated while patients are immunodeficient, but this strategy will not treat the underlying immunodeficiency (Answer D is incorrect).

7. Answer: B

Answer B is correct because minocycline-induced lupus usually develops after years of exposure. Answer A is incorrect because the risk of minocycline-induced lupus is very low. Answer C is incorrect because the incidence of drug-induced lupus is equal between males and females. Answer D is incorrect because laboratory testing is not recommended in patients who have no signs/symptoms of the disease.

8. Answer: A

Answer A is correct because the regimen consists of two NRTIs and an integrase inhibitor. Another possible combination includes two NRTIs and a PI. Answers B–D are incorrect because they contain three NRTIs.

9. Answer: B

Answer B is correct because the mother’s disease is well controlled; thus, the infant would need only 4 weeks of zidovudine prophylaxis. Answers C and D are

incorrect because nevirapine is not necessary for children born to women whose disease is well controlled on their antiretroviral regimen. Answer A is incorrect because antiretroviral prophylaxis is recommended to all infants born to HIV-positive mothers, regardless of the viral load.

10. Answer: B

Answer B is correct because pimecrolimus can cause stinging/burning on application, especially when beginning use. Answer A is incorrect because topical calcineurin inhibitors do not cause skin atrophy. Answer D is incorrect; serum concentration monitoring is not recommended because systemic absorption is minimal. Answer C is incorrect because pimecrolimus can be used both during flares and as maintenance.

11. Answer: A

Answer A is correct because anakinra is usually considered first-line therapy for systemic JIA. Answers B and C are incorrect because both etanercept and abatacept are recommended for JIA without systemic features. Answer D is incorrect because rituximab use is usually reserved for refractory disease.

12. Answer: B

Answer B is correct because tuberculosis testing is recommended before initiating biologic agents, given that they can lead to reactivation of latent disease. Answers A, C, and D are incorrect because testing for methicillin resistant *S. aureus*, CMV, or hepatitis C is not required.

NEPHROLOGY

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Learning Objectives

1. Differentiate between treatment strategies for primary nephrotic syndrome.
2. Develop a plan for managing the long-term complications of nephrotic syndrome.
3. Identify the different grades of hydronephrosis and the grades for which treatment is indicated.
4. Determine which alkalizing agent may be appropriate for a given subset of renal tubular acidosis.
5. Identify acute kidney injury (AKI) in infants and children and know which AKI criteria are correctly applied to neonates versus children.
6. Explain to caregivers the management of common comorbidities in children with chronic kidney disease.
7. Propose empiric therapy and therapy modifications in accordance with culture results for a child with a peritoneal dialysis catheter infection.
8. Summarize the differences between atypical and typical hemolytic uremic syndrome and explain the different treatment approaches to each.

Abbreviations

ACEI	Angiotensin-converting enzyme inhibitor
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
BUN	Blood urea nitrogen
CAP	Continuous antibiotic prophylaxis
CI	Confidence interval
CKD	Chronic kidney disease
CNI	Calcineurin inhibitor
CRRT	Continuous renal replacement therapy
ED	Emergency department
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
FSGS	Focal segmental glomerulosclerosis
GFR	Glomerular filtration rate
GH	Recombinant human growth hormone
GI	Gastrointestinal
HD	Hemodialysis
HR	Hazard ratio
HUS	Hemolytic uremic syndrome
ICU	Intensive care unit
IDMS	Isotope dilution mass spectroscopy
iPTH	Intact parathyroid hormone
IFN	Interferon
IL	Interleukin

ISPD	International Society for Peritoneal Dialysis
KDIGO	Kidney Disease: Improving Global Outcomes
MCNS	Minimal change nephrotic syndrome
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>
NGAL	Neutrophil gelatinase-associated lipocalin
NSAID	Nonsteroidal anti-inflammatory drug
PD	Peritoneal dialysis
PTH	Parathyroid hormone
RAAS	Renin-angiotensin-aldosterone syndrome
RBC	Red blood cell
REMS	Risk evaluation and mitigation strategies
RIFLE	Risk of renal dysfunction, injury to the kidney, failure of kidney function, loss of kidney function, and end-stage renal disease.
RTA	Renal tubular acidosis
SCr	Serum creatinine
SRNS	Steroid-resistant nephrotic syndrome
STEC	Shiga toxin-producing <i>Escherichia coli</i>
TIN	Tubulointerstitial nephritis
UPJ	Ureteropelvic junction
UTI	Urinary tract infection
VUR	Vesicoureteral reflux

Self-Assessment Questions

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

1. A 7-year-old boy on week 6 of prednisone therapy for minimal change nephrotic syndrome (MCNS) presents to the clinic. His dose has been tapered to 40 mg/m²/day on alternate days. His proteinuria has resolved, but he has persistent hypertension in the 95th percentile for age. He has been on both salt and water restriction since the diagnosis. Which is the best approach to initiating antihypertensive medication therapy?
 - A. Enalapril 0.1 mg/kg/dose by mouth twice daily.
 - B. Atenolol 0.5 mg/kg/dose by mouth twice daily.
 - C. Amlodipine 0.1 mg/kg/dose by mouth daily.
 - D. Lisinopril 0.3 mg/kg/dose by mouth daily.
2. A 16-year-old female adolescent presents with frequently relapsing steroid-dependent nephrotic syndrome. She is being initiated on intravenous rituximab after having been on corticosteroids for the past 6 months. What baseline monitoring parameter is recommended by KDIGO?

- A. Serum creatinine.
 - B. Hepatitis B surface antigen.
 - C. Varicella titer.
 - D. Purified protein derivative skin test.
3. Which patient is the most appropriate candidate for antibiotic prophylaxis?
- A. 2-week-old boy with unilateral low-grade hydronephrosis.
 - B. 1-day-old boy with antenatal hydronephrosis now with neonatal oliguria.
 - C. 11-day-old girl with renal bladder ultrasonography showing grade II hydronephrosis.
 - D. 6-week-old girl with antenatal hydronephrosis now with voiding cystourethrography showing grade IV vesicoureteral reflux (VUR).
4. A 4-year-old boy with MCNS is receiving prednisone 1 mg/kg every other day. He is due for his 4-year-old vaccines (measles, mumps, and rubella [MMR]; diphtheria and tetanus toxoids and acellular pertussis vaccine [DTaP]; inactivated poliovirus vaccine; and varicella). The patient's pediatrician asks which vaccines should be given. Which is the most appropriate response to give the pediatrician?
- A. Approve DTaP and inactivated poliovirus vaccine but let the physician know to hold varicella and MMR while the patient is receiving steroids.
 - B. Approve all the vaccines.
 - C. Tell the physician to hold all vaccines until the patient has been off steroids for 1 month.
 - D. Tell the physician that only DTaP is safe and that all the others should be held.
5. A 4-month-old boy (weight 3.5 kg) presents with failure to thrive, weakness, and polyuria. He is given a diagnosis of type I distal renal tubular acidosis (RTA) in keeping with the following laboratory values: urine pH 6.5, urine sodium 30 mEq/L, urine potassium 40 mEq/L, urine chloride 20 mEq/L, serum sodium 142 mEq/L, potassium 2.8 mEq/L, and bicarbonate 9 mEq/L. Ultrasonography reveals the presence of nephrocalcinosis. Which medication would best be considered first-line therapy for correcting these laboratory values?
- A. Hydrochlorothiazide 1 mg/kg/dose by mouth twice daily.
 - B. Spironolactone 2 mg/kg/dose by mouth once daily.
 - C. Sodium bicarbonate 1-mEq/mL solution, 4 mEq/kg/dose by mouth four times daily.
 - D. Potassium citrate and citric acid (Cytra-K) crystals, 2 mEq/kg/dose by mouth twice daily.
6. A 3-year-old girl (height 36 inches, weight 14 kg) presents to the clinic. Her serum creatinine (SCr), measured with isotope dilution mass spectroscopy (IDMS), is 0.7 mg/dL. Which is the most accurate calculation of her creatinine clearance (CrCl) with the modified Schwartz equation?
- A. 21 mL/minute/1.73 m².
 - B. 28 mL/minute/1.73 m².
 - C. 54 mL/minute/1.73 m².
 - D. 72 mL/minute/1.73 m².
7. A 9-year-old boy presents with chronic kidney disease (CKD). He is admitted to rule out a urinary tract infection (UTI). He has been febrile for the past 2 days, and his mother notes that his urine has been darker and cloudy. On admission, his serum phosphorus concentration is 6.2 mg/dL and his serum calcium concentration 10.8 mg/dL. He is taking calcium carbonate 500 mg 3 tablets by mouth three times daily with meals. Which statement is most appropriate?
- A. The patient does not seem to like the taste of calcium carbonate and is nonadherent to his treatment; suggest switching to calcium acetate capsules.
 - B. The patient's calcium phosphorus product is greater than 65 mg²/dL², and he should be changed to a non-calcium-based phosphorus binder such as sevelamer hydrochloride.
 - C. Once the patient's serum calcium concentration is corrected for his chronically low albumin, his calcium phosphorus product will be at goal; no change in therapy is needed.
 - D. Decrease the patient's calcium carbonate to 2 tablets by mouth three times daily with meals; his calcium concentration is mildly increased.

8. A 1-year-old boy, born at 26 weeks' gestational age and now weighing 9 kg, is awaiting a liver transplant for total parenteral nutrition cholestasis/short bowel syndrome resulting from severe necrotizing enterocolitis. Over the past 3 months, his renal function has declined. He is currently admitted for peritoneal dialysis (PD) catheter placement and initiation of outpatient PD. The nephrologist obtained a serum 25-hydroxyvitamin D (isotope dilution mass spectroscopy [IDMS]) concentration, which was low at 11 nmol/L, and an intact parathyroid hormone (iPTH), which was high at 670 pg/dL. She would like to start vitamin D supplementation. Which product is the best recommendation for this patient?
- Calcitriol 1 mcg/mL oral solution and ergocalciferol 8000 international units/mL to address the hypovitaminosis D and the high iPTH.
 - Ergocalciferol 8000 international units/mL oral solution, because it is affordable and easy to find.
 - Paricalcitol 1-mcg capsules, because it causes less hypercalcemia and less increase in calcium phosphorus product.
 - Cholecalciferol 400 international units/mL oral solution, because it tastes better.
9. A 5-year-old with stage 5 CKD resulting from typical hemolytic uremic syndrome (HUS) is maintained on PD. She experienced muscle aches, fatigue, and fevers and exhibited cloudy effluent last week and was started empirically on cefepime monotherapy. Today, 6 days after the initiation of antibiotics, the nephrologist calls because the culture now also has fungal elements. You want to recommend fluconazole. The *Pediatric & Neonatal Dosage Handbook* fluconazole monograph states "Dosing Adjustment in Renal Impairment" that there is only an adjustment for a CrCl of 50 mL/minute or less (not on dialysis): administer 50% of the recommended dose. It also states: "Patients receiving hemodialysis: Administer 100% of recommended dose after each dialysis treatment." Which best describes another reliable source of dosing information for PD?
- The *Nelson Textbook of Pediatrics*.
 - The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.
 - Epocrates.
 - The International Society for Peritoneal Dialysis (ISPD) guidelines.
- Questions 10 and 11 pertain to the following case.*
- A 7-year-old girl has been undergoing PD for the past 6 months because of bilateral Wilms tumor. She has a Broviac catheter for her chemotherapy and a planned bone marrow transplant. She has a history of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in her Broviac catheter but has not previously had a PD catheter infection. The PD catheter is now draining cloudy effluent, and it is being sent for culture.
10. Which empiric regimen is best for her?
- Give cefepime intraperitoneally in a 125-mg/L loading dose.
 - Give cefazolin intraperitoneally in a 500-mg/L loading dose plus gentamicin intraperitoneally in a 8-mg/L loading dose.
 - Give vancomycin intraperitoneally in a 1000-mg/L loading dose plus cefepime intraperitoneally in a 500-mg/L loading dose.
 - Hold off on antibiotics and wait for culture results.
11. The nephrologist also comments that the patient's serum calcium has been trending upward, with today's value at 10.2 mg/dL. The patient is receiving a standard PD fluid, as well as sevelamer carbonate 800 mg by mouth three times daily with meals as her phosphate binder. Which would best be recommended?
- Start outpatient pamidronate in the infusion clinic every month.
 - Shorten dwell time to prevent calcium from absorbing as much.
 - Change to a low-calcium PD solution and repeat serum phosphorus and calcium determinations in 2 weeks.
 - Increase the frequency of PD exchanges to remove more solute.

12. A 2-year-old girl presents to the pediatric intensive care unit (ICU) with severe renal failure. She is being started on continuous renal replacement therapy (CRRT), and her medical history is significant for a 1-week history of gastroenteritis and bloody stools. Her parents state that she was fine until 24 hours before admission, when she seemed very sleepy and was too tired to get out of bed. She has a working diagnosis of HUS, though stool studies are pending. The pediatric ICU fellow asks about using eculizumab (Soliris) for this patient. Which is the most appropriate response?
- A. Eculizumab is not indicated for patients with typical HUS.
 - B. Eculizumab, which costs thousands of dollars per dose, should not be used as first-line therapy.
 - C. Eculizumab can increase the risk of infection, and because the patient is likely already infected with *Escherichia coli*, it may worsen her course.
 - D. The CRRT circuit will remove eculizumab, so therapy may not be started until she is off CRRT.
13. A 3-month-old boy (weight 6 kg) presents with atypical HUS. He has been started on plasmatherapy while the team awaits eculizumab insurance approval. Which drug would best be administered before starting eculizumab therapy?
- A. Prevnar-13, because of increased risk of streptococcal infection.
 - B. Menactra, because of increased risk of meningococcal infection.
 - C. Varivax, because of increased risk of varicella infection.
 - D. FluMist, because of increased risk of influenza infection.
14. A 16-year-old female adolescent was started on amoxicillin 500 mg by mouth three times daily as an outpatient for strep throat. After a few days of the antibiotic, she began to experience acute flank pain and urinary urgency, and her urine became darker and took on a pink tint. She also takes drospirenone/ethinyl estradiol (Yasmin) oral contraceptive and loratadine 10 mg by mouth daily and uses topical azelaic acid (Azelex) for acne. The emergency department (ED) has discontinued her amoxicillin for presumed tubulointerstitial nephritis (TIN). Which is the most effective way to treat her strep throat?
- A. Azithromycin.
 - B. Cefuroxime.
 - C. Clindamycin.
 - D. Clarithromycin.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5, 1.8
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.4

I. NEPHROTIC SYNDROME

A. Pathophysiology

1. Proteinuria and hypoalbuminemia caused by alterations in the glomerular filtration barrier
 - a. The glomerular filtration barrier comprises three layers: the fenestrated endothelium, the glomerular basement membrane, and the epithelial foot processes. The pores between the foot processes are closed by the slit diaphragm, which is a thin membrane.
 - b. Filtration of macromolecules across the glomerular capillary wall is controlled by charge-selectivity and size-selectivity.
 - c. In minimal change disease there is a loss of anionic charge and epithelial podocyte effacement.
 - d. Glomerular damage may occur with structural injury, resulting in an increase in the number of large pores in the glomerular basement membrane. This permits movement of proteins that typically could not cross the filtration barrier. These proteins include large molecules such as IgG.
2. Edema is caused by a decrease in plasma oncotic pressure resulting from the loss of serum albumin. Although these mechanisms are still not well understood, edema may be a result of intrinsic causes or excess vasopressin expression. Activation of the renin-angiotensin-aldosterone system (RAAS) results in the reabsorption of sodium.
3. Hyperlipidemia occurs, including increased concentrations of very low-density lipoprotein (VLDL), intermediate-density lipoprotein, and low-density lipoprotein (LDL), together with increases in serum cholesterol and triglycerides. Hyperlipidemia is believed to be related to the low plasma albumin concentration, low oncotic pressure, and impaired catabolism of apolipoprotein B and VLDL chylomicrons.

B. Epidemiology

1. Incidence in the United States is estimated at 2.7 new cases per 100,000 children per year.
2. Cumulative prevalence is 16 per 100,000 children.
3. Male/female ratio is 2:1 in childhood.
4. Incidence wanes by adolescence.
5. Mean age at onset is 3.4 years in Asians and 4.2 years in Europeans.
6. African American and Hispanic children have increased disease incidence, more severe disease, and poorer prognosis.

C. Cause

1. Decrease in immune responsiveness or disorders affecting T-lymphocyte function
2. Possible increased expression of interleukin (IL)-2 on T lymphocytes
3. Increases in IL-8, IL-13, insulin-like growth factor-1, transforming growth factor beta and interferon (IFN) gamma
4. Abnormalities in nephrin, a protein component of the glomerular filtration barrier, expression or distribution
5. Increased circulating “vascular permeability factor”
6. Genetic causes may play a role in many forms of nephrotic syndrome.

D. Diagnosis

1. Diagnosis is often based on symptoms (proteinuria, hypoalbuminemia, and edema), and therapy with corticosteroids (usually prednisone) is initiated without the need for renal biopsy. This is because of the prognostic value of steroid responsiveness in children. Ninety-five percent of children will respond to steroids and will have a strong response within the first 4 weeks.
2. Laboratory findings
 - a. Reduction in plasma protein
 - b. Hypoalbuminemia ($<2.5\text{mg/dL}$)
 - c. Increased total cholesterol and triglycerides
 - d. Hyponatremia
 - e. Hypocalcemia
 - f. Urine protein loss ($\geq 300\text{ mg/dL}$ or 3+ protein on urine dipstick)
 - g. Urine albumin loss ($\geq 200\text{ mg/mmol}$)
3. Renal biopsy is the gold standard for diagnostic evaluation and should be performed if a biopsy result is expected to alter treatment and/or if additional prognostic information is needed.
4. Biopsy is not needed for children under the following circumstances
 - a. Steroid-sensitive nephrotic syndrome and younger than 12 years of age
 - b. Children with poststreptococcal glomerulonephritis
 - c. PLA2Rab+ membranous (especially with normal glomerular filtration rate [GFR])
 - d. MPO+ or PR3+ ANCA vasculitis
 - e. Anti-glomerular basement membrane disease
 - f. Alport disease
 - g. Fabry disease
 - h. Familial focal and segmental glomerulosclerosis in families with well-characterized mutations
 - i. Biopsy contraindicated as judged by history, physical exam, and laboratory testing
 - j. Systemic lupus erythematosus
5. Assessment of proteinuria is a component of long-term follow-up for the disease process. Protein/creatinine ratio or albumin/creatinine ratio of a random urine sample or the first morning urine sample is often used for assessment. Children with uncontrolled nephrotic syndrome will typically have a first morning or *24-hr protein/creatinine ratio of 2 g/kg (or 200 mg/mmol or greater than or equal to 3+ dipstick) or greater.
6. Genetic testing should be considered for steroid-resistant nephrotic syndrome, which may help guide immunosuppression choice. Genetic testing should particularly be considered for infantile forms if there is a positive family history of kidney disease and/or the patient has syndromic features.

E. Classification

1. Primary (idiopathic) nephrotic syndrome accounts for 90% of diagnoses. There are three main subsets of primary disease. (Note that many authors will define subsets of idiopathic nephrotic syndrome by steroid-responsiveness, which can lead to confusion.)
 - a. Minimal change nephrotic syndrome (MCNS) represents the most common subset of children and accounts for about 85% of cases. Electron microscopy reveals fusion of the epithelial foot processes.
 - b. Focal segmental glomerulosclerosis (FSGS) occurs in 10%–15% of all cases. In FSGS, scar tissue develops in segments of some glomeruli, eventually leading to extensive global glomerular sclerosis and tubular atrophy.
 - c. Membranous nephropathy, involving diffuse thickening of the glomerular capillary walls, accounts for only 4% of cases in children.

2. Secondary causes of nephrotic syndrome account for the remaining 10% of all diagnoses in children. There are three main subtypes of disease and several miscellaneous causes.
 - a. Infections: Hepatitis B, hepatitis C, HIV, malaria, toxoplasmosis, and syphilis
 - b. Drugs: Nonsteroidal anti-inflammatory agents (NSAIDs), pamidronate, rifampin, lithium, heroin, IFN, and gold
 - c. Malignancies: Leukemia and lymphoma
 - d. Miscellaneous causes: Systemic lupus erythematosus, IgA nephropathy, diabetes mellitus, and mesangioproliferative glomerulonephritis. For all four of the previously listed secondary causes, the prognosis is considered poor.
3. Complete remission is defined as a first morning or *24-h protein/creatinine ratio of 200 mg/g (or 20 mg/mmol or negative trace dipstick) or less on three or more consecutive occasions.
4. Partial remission is defined as a first morning or *24-h protein/creatinine ratio greater than 200 mg/g but less than 2 g/g (or greater than 20 and less than 200 mg/mmol) and, if available, serum albumin 30 g/L (3 g/dL) and greater.
5. A relapse is defined as recurrence of nephrotic range proteinuria. In children, relapse is commonly assessed by urine dipstick and is defined as dipstick 3+ and greater for 3 consecutive days.
6. Steroid-sensitive nephrotic syndrome is defined as complete remission after 4 weeks of prednisone or prednisolone at standard dose.
7. Infrequent relapsing nephrotic syndrome is defined as fewer than two relapses per 6 months within 6 months of disease onset or fewer than four relapses per 12 months in any subsequent 12 month period.
8. Frequent relapsing nephrotic syndrome (FRNS) is defined as two or more relapses per 6 months within 6 months of disease onset or four or more relapses per 12 months in any subsequent 12-month period.
9. Steroid-dependent nephrotic syndrome (SDNS) is defined as two consecutive relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation.
10. Steroid-resistant nephrotic syndrome (SRNS) is defined as lack of complete remission at 4 weeks of therapy with daily prednisone or prednisolone at standard dose.
11. Late responder is defined as complete remission at 6 weeks.
12. Calcineurin inhibitor responsive SRNS is defined as partial remission after 6 months of treatment and/or complete remission after 12 months of treatment with a calcineurin inhibitor at adequate doses and/or levels.
13. Calcineurin inhibitor resistant SRNS is defined as absence of partial remission after at least 6 months of treatment with a calcineurin inhibitor at adequate doses and/or levels.
14. Multidrug-resistant SRNS is defined as absence of complete remission after 12 months of treatment with two mechanistically distinct glucocorticoid sparing agents at standard doses.
15. Secondary SRNS is defined as a steroid-sensitive nephrotic syndrome patient at disease onset who at a subsequent relapse fails to achieve remission after 4 weeks of therapy with daily prednisone or prednisolone at standard dose.

F. General Treatment Concepts

1. Treatment choice depends on the exact disease type (primary vs. secondary), subset of disease, and previous response to therapies. Treatment of secondary nephrotic syndrome will not be covered. The KDIGO guidelines provide a workflow diagram to help direct decision making for treatment options in primary nephrotic syndrome (Figure 1).

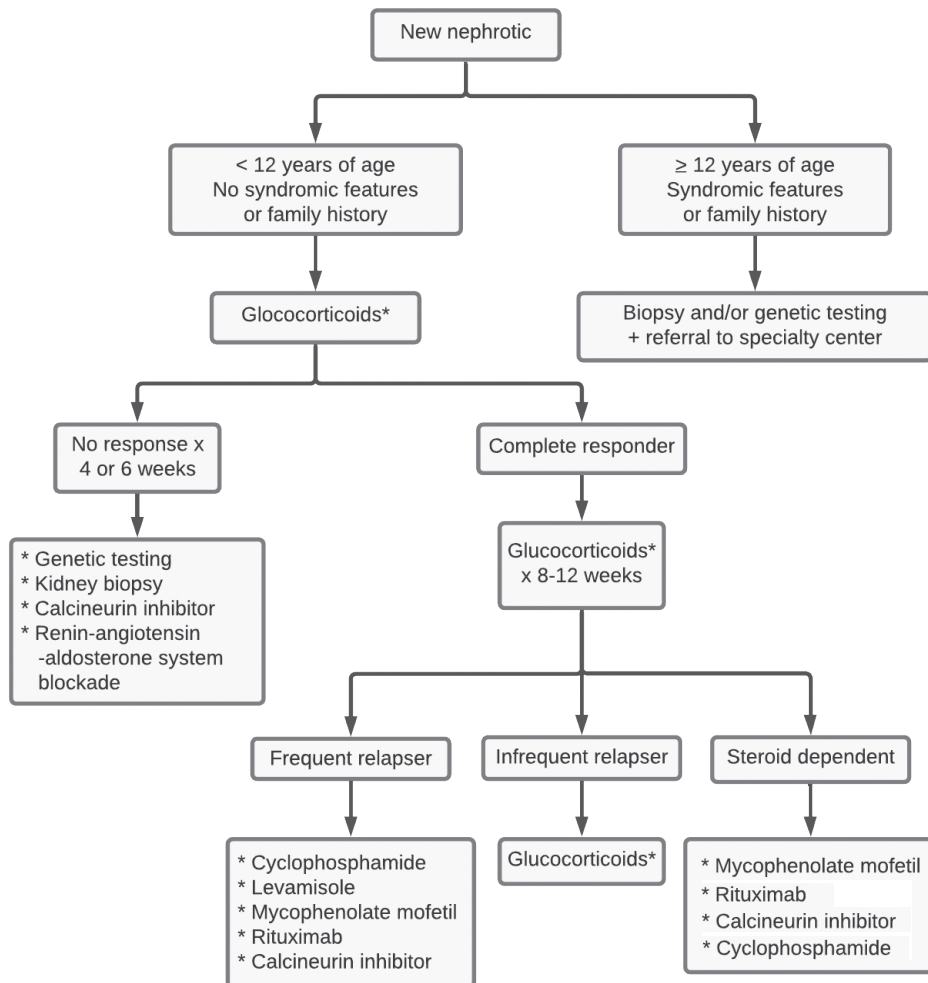


Figure 1. Kidney Disease: Improving Global Outcomes guidelines. Adapted with permissions from: Kidney Int 2021;100:S1-276.

2. For the initial treatment of nephrotic syndrome, KDIGO recommends oral glucocorticoids for 8–12 weeks. There are two regimens that may be used.
 - a. Daily oral prednisone/prednisolone 60 mg/m²/day or 2 mg/kg/day (maximum 60 mg/day) for 4 weeks, followed by alternate-day prednisone/prednisolone 40 mg/m²/day or 1.5 mg/kg/day (maximum 50 mg) for another 4 weeks
 - b. Daily oral prednisone/prednisolone 60 mg/m²/day or 2 mg/kg/day (maximum 60 mg/day) for 6 weeks, followed by alternate-day prednisone/prednisolone 40 mg/m²/day or 1.5 mg/kg/day (maximum 50 mg) for another 6 weeks
3. The KDIGO guidelines recommend relapses in steroid-sensitive nephrotic syndrome should be treated with oral prednisone/prednisolone at a single daily dose of 60 mg/m²/day or 2 mg/kg/day (maximum 60 mg/day) until the child achieves full remission as defined previously.

4. The KDIGO guidelines recommend alkylating agents (most commonly cyclophosphamide in the United States), calcineurin inhibitors (CNIs), or mycophenolate mofetil for steroid sparing in frequently relapsing steroid-sensitive nephrotic syndrome. Rituximab is recommended only for steroid-dependent, steroid-sensitive patients who have frequent relapses despite optimal combinations of prednisone and corticosteroid-sparing agents and/or who have had significant adverse effects.
 - a. For children with frequently relapsing and steroid-dependent nephrotic syndrome who are currently taking alternate day glucocorticoids or are off glucocorticoids, the KDIGO 2021 guidelines recommend that daily glucocorticoids 0.5 mg/kg/day be given during episodes of upper respiratory tract and other infections for 5–7 days to reduce the risk of relapse.
 - b. For children with frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome without glucocorticoid toxicity, the same glucocorticoid regimen may be used in subsequent relapses.
 - c. For children with frequently relapsing nephrotic syndrome without steroid glucocorticoid-related adverse effects, low-dose alternate day oral prednisone/prednisolone (ideally 0.5 mg/kg/day or less) can be used to prevent relapse.
5. KDIGO recommends that children with frequently relapsing nephrotic syndrome who develop glucocorticoid-related adverse effects and that all children with steroid-dependent nephrotic syndrome receive glucocorticoid sparing agents rather than no treatment or continuation of glucocorticoid-based monotherapy.
 - a. Ideally, children should be in remission with glucocorticoids prior to initiating glucocorticoid-sparing agents such as oral cyclophosphamide, levamisole, mycophenolate mofetil, rituximab, or CNIs. Co-administration is recommended with a glucocorticoid for 2 or more weeks following initiation of glucocorticoid-sparing treatment.
 - b. Selection of the glucocorticoid-sparing agent is a decision that should be patient specific taking into consideration resources, adherence, adverse effects, and patient preference.
 - i. Oral cyclophosphamide and levamisole (outside of the United State only) may be preferable in frequently relapsing nephrotic syndrome.
 - ii. Mycophenolate mofetil, rituximab, and CNIs (tacrolimus, cyclosporine), and cyclophosphamide may be preferable to glucocorticoid-sparing therapies in children with steroid-dependent nephrotic syndrome.
6. Cyclosporine or tacrolimus are recommended as initial second line therapy for children with steroid-resistant nephrotic syndrome.
7. In patients with a relapse of nephrotic syndrome after complete remission, recommended treatment options include oral corticosteroids, return to previous successful immunosuppressive agent, and use of an alternative immunosuppressive agent to minimize potential cumulative toxicity.
8. For children specifically diagnosed with membranous nephropathy (MN), KDIGO suggests the following
 - a. Perform a kidney biopsy
 - b. Treat with prednisone/prednisolone for at least 8–12 weeks at doses used for idiopathic nephrotic syndrome.
 - c. Rituximab or CNIs may be considered at standard doses.
 - d. It is suggested that children with MN be treated at an expert center.
9. Children with steroid-resistant nephrotic syndrome should be treated with a renin-angiotensin-aldosterone system inhibitor, which is further covered later in the chapter.
10. Agents that are being evaluated for treatment of nephrotic syndrome in adults and children but that are not yet included in the KDIGO guidelines include monoclonals (abatacept, adalimumab, daratumumab, fresolimumab, obintuzumab, and ofatumumab) and steroids (adrenocorticotrophic hormone and deflazacort).
11. Despite maximized medical management, patients with continued poor response to therapy may ultimately require a nephrectomy or renal transplant.

G. Pharmacotherapy of Nephrotic Syndrome

1. Prednisone

- a. Mechanism of action: Broad suppression of the immune system, including down-regulation of IL-2 and interferon gamma, sequestration of T lymphocytes in the bone marrow, and decreased production of inflammatory cytokines
- b. Dosing regimens: Vary greatly by prescriber/center and syndrome subset
 - i. Response to steroid therapy in the first 8–12 weeks of treatment will occur in about 90% of children, fulfilling the criteria for diagnosis of MCNS.
 - ii. The 2021 KDIGO clinical practice guideline for glomerulonephritis recommends the two steroid regimens provided in previously in F 2. These two regimens are considered equivalent because of insufficient evidence to recommend one as preferred.
 - (a) Note that the International Study of Kidney Disease in Children guidelines allow a higher maximum daily dose of 80 mg for the first 4 weeks of therapy and offer alternative tapering regimens.
 - (b) In some studies of nephrotic syndrome, daily dosing has been split into two or three divided doses.
 - iii. A 2012 study suggests that 5 months of prednisone, versus 3 months, reduces the risk of relapse (J Nephrol 2012;25:394-400). Some studies have used durations of up to 12 months after an initial episode, and treatment varies considerably by treatment center. This longer treatment duration was recently called into question by new controlled trials. The 2021 KDIGO guidelines recommend against initial treatment beyond 12 weeks.
 - iv. Several recent studies have compared overall corticosteroid exposure during induction with outcomes using body-weight versus body-surface area dosing strategies as recommended in KDIGO (Pediatr Nephrol 2016;31:595-604; Clin Exp Nephrol 2020;24:622-9; among others). These studies have found higher cumulative exposure in children dosed using body-surface area but no difference in relapse rate. Due to low patient enrollment and lack of long term follow-up, further studies are needed.
 - v. Steroids are often used as adjuvant therapy in children with steroid-resistant forms of nephrotic syndrome as well.
 - (a) Corticosteroid doses have ranged widely, up to 2 mg/kg/day of prednisone. KDIGO does provide specific recommendations (covered previously) though other approaches may be used.
 - (b) Intravenous pulse dose methylprednisolone has been used at doses of 10–30 mg/kg/day with variable frequencies and intervals.
 - (c) Intravenous therapy may be advantageous over enteral therapy during disease flare due to decreased enteral absorption secondary to gut wall edema.
 - (d) Steroids are associated with high adverse event rates. Both FSGS and MN may be minimally responsive; therefore, steroid exposure should be minimized when possible.
- c. Tapering of steroid treatment is recommended in the KDIGO guidelines, but it also varies widely by disease type, prescriber, and patient response. Some centers discontinue steroids abruptly at the end of the treatment period with no wean, and others wean over 2–4 weeks.
- d. Caution: hypertension (present in 13%–51% of children with nephrotic syndrome), obesity and growth issues, striae, cushingoid appearance, and infection, including spontaneous bacterial peritonitis and osteopenia

2. Cyclophosphamide

- a. Mechanism of action: Alkylating agent with nonspecific immunosuppressive effects. Mechanism of action not well described in nephrotic syndrome.

- b. Dosing regimens: Vary by prescriber/center, syndrome subset, and study
 - i. Intravenous therapy is not recommended as the preferred route for this agent. When given, intravenous dosing regimens have varied, but the most common is 500 mg/m² per dose, given over 4 hours at monthly intervals.
 - ii. Both the KDIGO and the International Study of Kidney Disease in Children guidelines recommend oral dosage forms for the treatment of steroid-dependent or frequently relapsing nephrotic syndrome. Cyclophosphamide treatment should not be started until the child is in complete remission with glucocorticoids. The maximum dose currently recommended for oral cyclophosphamide is 2 mg/kg/day for 12 weeks (total dose 168 mg/kg), which is lower than the gonadotoxic dose of 300 mg/kg. A second course with alkylating agents cannot be used.
 - c. Younger children appear to have a poorer response to cyclophosphamide. This could be partly because use of body weight may underexpose young children. Younger children may also have immature immune systems that respond differently to cytotoxic treatment. Genetic polymorphisms may also play a role in response to therapy.
 - d. Cumulatively, cyclophosphamide studies show that only about one-third of pediatric patients will achieve long-term remission.
 - e. Caution: fertility issues, neutropenia, leukopenia, alopecia, amenorrhea, and infection risk. Children may struggle with frequent outpatient infusion clinic attendance if intravenous therapy is used.
 - f. Fluid overload can be a concern when intravenous cyclophosphamide is used because of the need for hydration to prevent renal and bladder toxicity.
 - g. Requires hazardous drug handling precautions
 - h. Caution in patients with childbearing potential
3. Cyclosporine
- a. Mechanism of action: Inhibits IL-2–mediated T-cell activation. Direct effects on podocyte architecture, intracellular signaling pathways, glomerular blood flow, and glomerular basement membrane permselectivity.
 - b. Dosing regimens: Vary greatly by prescriber/center and syndrome subset. The most common dosing regimens cited in studies are 150 mg/m²/day or 4–6 mg/kg/day in two divided doses. The KDIGO 2021 guidelines suggest a dose range of only 4–5 mg/kg/day at initiation in two divided doses per day, a trough goal of 60–150 ng/mL, and to aim for the lowest level possible to maintain remission and minimize toxicity.
 - c. Adverse effects, drug–drug interactions, and formulations can be found in the Solid Organ Transplantation chapter.
4. Tacrolimus
- a. Mechanism of action: Inhibits IL-2–mediated T-cell activation. Direct effects on podocyte architecture, intracellular signaling pathways, glomerular blood flow, and glomerular basement membrane permselectivity.
 - b. Dosing regimens: Vary greatly by prescriber/center and syndrome subset. The most common dosing regimens cited in studies include 0.05–0.2 mg/kg/day in two divided doses (starting dose 0.1 mg/kg/day per KDIGO). KDIGO 2021 guidelines suggest a trough goal of 5–10 ng/mL and to aim for the lowest level that maintains remission to avoid toxicity.
 - c. Adverse effects, drug–drug interactions, and formulations can be found in the Solid Organ Transplantation chapter.
5. Mycophenolate mofetil
- a. Mechanism of action: T and B lymphocytes, cell surface markers, and cytokine gene expression inhibition
 - b. Dosing regimens: Vary greatly by prescriber/center and syndrome subset. The most common dosing regimens cited in studies are 500–1200 mg/m²/day in two divided doses (maximum of 1 g per dose). KDIGO recommends a starting dose of 1200 mg/m²/day in divided doses.

- c. Target area under the curve greater than 50 mcg·hr/mL
 - d. Mycophenolate mofetil should be continued for at least 12 months because of risk of relapse upon discontinuation.
 - e. Conversion to mycophenolic acid analogs is allowed for children who experience significant abdominal pain despite lack of prospective studies with this formulation.
 - f. Adverse effects, drug–drug interactions, and formulations can be found in the Solid Organ Transplantation chapter.
6. Rituximab
- a. Mechanism of action: Not fully understood but hypothesized to be related to B-cell depletion
 - b. Dosing regimens: 375 mg/m² intravenous given once weekly or at intervals, depending on B-cell depletion or symptoms. Other dosing regimens have been studied, and there is much interest in further clarifying whether higher compared with lower dosage regimens may yield improved results (Kidney Int 2020;97:393-401).
 - c. May be considered for patients with frequently relapsing, steroid-dependent, or steroid-resistant disease, though its exact place in therapy is still being defined and is under active study.
 - d. Caution: Infection, rituximab antibody formation, bone marrow suppression, and infusion reactions.
 - i. The package insert contains a black box warning on fatal infusion reactions, which can occur with the first dose and can be life threatening.
 - ii. Specific infusion rates are recommended in the package insert for the first dose versus subsequent doses.
 - iii. Monitoring and discontinuation instructions are also available and should be reviewed before a patient is started on rituximab therapy.
 - iv. Rituximab therapy may also alter response to vaccines. Hepatitis B surface antigen, hepatitis B core antibody, and a QuantiFERON test for tuberculosis must be checked prior to initiation of therapy. The impact on live vaccines is not studied and it is recommended to avoid them before or during treatment. Nonlive vaccines may be given up to 4 weeks prior to initiation of therapy but should also not be given during therapy. Further studies are needed.
 - v. The manufacturer recommends that the infusion rate be titrated to minimize the risk of infusion toxicity. Pediatric-specific titration instructions are provided for patients with mature B-cell non-Hodgkins lymphoma/mature B-cell acute leukemia and could be extrapolated for management of nephrotic syndrome.
 - vi. Premedication with acetaminophen and an antihistamine is recommended in the package insert for all indications. Premedication with methylprednisone is recommended in the package insert for all U.S. Food and Drug Administration (FDA)–labeled indications; however, it is not specifically stated as a requirement for nephrotic syndrome (no FDA indication). Most clinical trials using rituximab for the treatment of nephrotic syndrome have pretreated patients with intravenous methylprednisolone.
 - vii. KDIGO recommends that CD20 levels should be monitored where available.
 - viii. Monitoring IgG levels before and after rituximab is suggested by KDIGO to capture children at risk for developing infection and target those who may benefit from immunoglobulin replacement.
 - e. Rituximab is not on the National Institute for Occupational Health and Safety list and does not require handling precautions.
 - f. Female patients of childbearing age should use effective contraception while receiving rituximab and for 12 months after treatment.
7. Levamisole
- a. Not FDA approved for use in the United States. Although originally on the U.S. market and approved as an anthelmintic, it was withdrawn in 1999 because of its unacceptable adverse event rate.

- b. Despite lack of FDA approval, research continues with levamisole outside the United States, and KDIGO continues to suggest it as a possible treatment option (no direct comparator data with oral cyclophosphamide) and may be an alternative for children in other countries.

II. COMORBIDITIES IN PEDIATRIC NEPHROTIC SYNDROME

A. Nephrotic Edema

1. Edema and weight gain are common in children with nephrotic syndrome.
 - a. Edema may promote hypertension (intrinsic defect in sodium excretion by the kidneys).
 - b. Edema may cause pain and discomfort and promote infection (cellulitis, peritonitis).
2. Loop diuretics (furosemide, torsemide, bumetanide) are the mainstay of treatment.
 - a. Resistance is common, and higher doses or more frequent dosing may be necessary.
 - b. Agents other than furosemide may confer benefit but this is not proven in pediatric specific literature.
3. Combination therapy may be attempted
 - a. Loop diuretic plus a thiazide-like diuretic may overcome resistance by blockade of sodium resorption at several sites within the nephron. If this is done, it is recommended to administer the thiazide diuretics 2–5 hours prior to the loop for maximum benefit.
 - b. Combination with potassium sparing diuretics may prevent hypokalemia.
4. Gastrointestinal absorption may be impaired due to intestinal wall edema.
 - a. Consideration may be made for intravenous dosing for the loop or both the loop and the thiazide diuretic.
 - b. Caution should be exercised with rapid administration of large doses of loop diuretic, which may increase the risk of ototoxicity or tinnitus.
5. Addition of albumin to loop diuretic therapy may improve intravascular volume, diuresis, and natriuresis but evidence is limited.
 - a. Some centers will admix diuretic and albumin together and run as a continuous infusion.
 - b. If given separate, some centers advocate for administration of the loop diuretic 1–2 hours after or into the albumin infusion.
 - c. Unfortunately, there is limited data available comparing infusion strategies, and this is a requested area of research by KDIGO.
6. Some patients may ultimately require or benefit from ultrafiltration or hemodialysis to manage severe edema.

B. Hypertension

1. Hypertension is present in 13%–51% of children with nephrotic syndrome. Blood pressure generally improves with remission.
2. There is up-regulation of the RAAS in response to hypovolemia, which leads to sodium and water retention. Blockade of the RAAS is known to delay the progression to end-stage renal disease (ESRD) in patients with proteinuria.
3. Pediatric blood pressure target is a 24-hour mean arterial pressure in the 50th percentile or less for age, sex, and height by ambulatory blood pressure monitoring.
4. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) are recommended as the first-line treatment for children with nephrotic syndrome. The dose should be maximized before moving on to other agents. Both fosinopril (5–10 mg/day) and enalapril (0.2–0.6 mg/kg/day) have been shown in prospective studies to decrease proteinuria in children with steroid-resistant nephrotic syndrome. Other ACEIs are frequently used as well. Currently, ARBs have not been formally studied but are often used.

5. KDIGO recommends frequent laboratory monitoring for patients taking ACEIs or ARBs, given that, especially during titration, these agents contribute to acute kidney injury or hyperkalemia. Potassium wasting or binding agents may be helpful in addressing hyperkalemia to facilitate the ongoing beneficial effects on proteinuria from these agents. ACEIs and ARBs should be held if acute volume depletion occurs, and caregivers should be counseled regarding this.
6. Sodium restriction, smoking cessation if pertinent, and physical activity may also be beneficial in blood pressure management.

C. Dyslipidemia

1. Dyslipidemia, a hallmark feature of nephrotic syndrome, may persist despite remission from the disease. Hyperlipidemia results from overproduction of VLDL, LDL as a result of low plasma albumin concentration, low oncotic pressure, and impaired catabolism of apolipoprotein B and VLDL chylomicrons and intermediate-density lipoprotein.
2. Limited data are available evaluating the use of statins in pediatric hyperlipidemia caused by nephrotic syndrome. Only fluvastatin, lovastatin, and simvastatin have been prospectively evaluated. Drug–drug interactions are common, particularly in children undergoing CNI therapy.
3. Despite the limited evidence in nephrotic syndrome, most pediatric centers use low-fat diets (less than 30% calories from fat, saturated fat less than 10% of calories, and less than 300 mg/day of dietary cholesterol) in patients 2 years of age and older with nephrotic syndrome and use statin therapy when fasting LDL concentrations are consistently greater than 130 mg/dL.
4. In the absence of guidelines specifically for children with nephrotic syndrome, most centers follow the 2011 National Heart, Lung, and Blood Institute (NHLBI) guidelines (Pediatrics 2011;128[Suppl 5]:S213-S256). A thorough review on how the NHLBI guidelines may be applied to children with nephrotic syndrome has been published recently (Pediatr Nephrol 2020;35:1601-19).
5. LDL apheresis is another treatment approach that may be used in some centers, though robust data are currently lacking, particularly in children younger than 5 years. A thorough review of dyslipidemia management in children with nephrotic syndrome was recently published (Pediatr Nephrol 2020;35:1601-19). This review includes a discussion about the role of LDL apheresis and pharmacotherapy, including the use of monoclonal agents. The previously mentioned review by Hari and colleagues in 2020 also summarizes how LDL apheresis may be utilized for children with nephrotic syndrome.

D. Thromboembolism

1. Thromboembolism develops in 2%–5% of children with nephrotic syndrome.
2. Children with nephrotic syndrome have urinary loss of proteins including antithrombin III and protein S, which inhibit clot formation.
3. There may also be increased production of factors such as fibrinogen which promote clot formation.
4. Volume depletion caused by dehydration or diuretics may further increase the risk of clot formation.
5. There are currently no drug studies evaluating anticoagulation in children with nephrotic syndrome.
 - a. Adult studies have evaluated aspirin and warfarin.
 - b. For acute clots, most centers use heparin- or warfarin-based regimens.
 - c. If heparin-based anticoagulation is used (including low-molecular-weight heparins), antithrombin III concentrations should be followed because of the risk of treatment failure.
6. The 2021 KDIGO guidelines address thromboembolism and prevention for adult patients but make no specific recommendations for children at this time. It remains unclear how much the algorithm and suggestions presented for adult patients can be extrapolated to the pediatric population, but the reader is referred to this for consideration.
7. Consultation with a hematology specialist is recommended.
8. The role of primary prevention is unclear.

E. Infection

1. Infections are common and can be life threatening in children with nephrotic syndrome.
 - a. The increased incidence of infections is thought to be caused by urinary loss of factors B and I, decreased IgG synthesis (as well as increased loss), and impaired T-cell function.
 - b. Many of the previously reviewed drug therapies also further increase the risk of infection and may impair response to childhood vaccinations if not timed appropriately.
2. Children with nephrotic syndrome appear to be at highest risk of UTIs, cellulitis, spontaneous bacterial peritonitis, pneumonia, and meningitis.
 - a. The organisms that most commonly cause infection are *Streptococcus pneumoniae* and *Haemophilus influenzae*.
 - b. Higher infection rates with these bacteria are thought to be because of the loss of factors B and I, which decreases opsonization and clearance of encapsulated microorganisms.
 - c. Increased vaccination against *S. pneumoniae* and *H. influenzae* has led to an increase in the relative frequency of gram-negative infections.
3. Vaccines in children with nephrotic syndrome
 - a. Children should have live vaccinations deferred until the prednisone dose is less than 2 mg/kg/day (max 20 mg) for 1 month and for 3 months after completion of therapy with cytotoxic agents such as cyclophosphamide.
 - b. Both live and inactivated vaccines should be withheld at least 6 months after therapy with anti-B-cell antibodies such as rituximab (Clin Infect Dis 2014;58:e44-100).
 - c. Live vaccines should be deferred for 1 month from completion of other daily immunosuppression, such as cyclosporine.
 - d. Patients with nephrotic syndrome, as well as the household contacts of children with nephrotic syndrome, should be counseled to receive the inactivated influenza vaccine yearly.
 - e. In addition to routine vaccination with the pneumococcal vaccine series, it is recommended that the 23-valent pneumococcal polysaccharide vaccine be administered to patients 2 years and older who have completed their pneumococcal vaccine series (MMWR 2010;59(RR11):1-24).
4. At this time there is no recommendation for long-term antibiotic prophylaxis in children with nephrotic syndrome.

F. Osteopenia/Vitamin D Deficiency

1. Vitamin D deficiency has been reported in children with active nephrotic syndrome. Vitamin D deficiency is caused by the urinary loss of vitamin D-binding protein, a carrier protein for 25-hydroxycholecalciferol, which may also cause secondary hyperparathyroidism. In addition, chronic glucocorticoid use can exacerbate osteopenia in these patients.
2. In 2016, the Midwest Pediatric Nephrology Consortium published the results of a multicenter longitudinal study of children (2–18 years) from 14 centers with incident idiopathic nephrotic syndrome (Pediatr Nephrol 2016;31:465-72). 25(OH)D concentrations were assessed at diagnosis and 3 months later. All patients had 25(OH)D concentrations less than 20 ng/mL at diagnosis. 25(OH)D concentrations were reassessed at a follow-up appointment 3 months after diagnosis. At the time of follow-up, 53% of patients had 25(OH)D concentrations below 20 ng/mL, and 33% were taking a vitamin D supplement. The authors found that supplemental vitamin D decreased the odds of 25(OH)D deficiency (odds ratio 0.2; 95% confidence interval [CI], 0.04–0.56), $p=0.005$.
3. In a randomized, placebo-controlled study of children with MCNS undergoing steroid treatment (Pediatr Nephrol 2006;21:350-4), the children (mean 4.6 ± 1.8 years old) took prednisolone 2 mg/kg/day (max 60 mg/day) $\times$ 4 weeks, followed by 2 mg/kg/day on alternate days for an additional 4 weeks. The children were randomized to receive placebo or vitamin D₃ 400 international units plus 1 g of elemental calcium per day. Although bone mineral density decreased in both the treatment and placebo groups, the decrease was significantly less in the vitamin D- and calcium-supplemented group ($4.6\% \pm 2.1\%$ vs. $13.0\% \pm 4.0\%$, respectively; $p<0.001$).

4. There are no formal recommendations on supplementation, but vitamin D concentration assessment should be considered, and supplementation should be initiated in children receiving high-dose glucocorticoids for prolonged periods.
5. A recent study (Pediatr Nephrol 2020;35:447-54) suggested that total 25(OH)D concentrations are unreliable in children with nephrotic syndrome with proteinuria. These authors suggest that free 25(OH)D may be more helpful to diagnose and guide therapy. Further studies are needed.

Patient Cases

Questions 1 and 2 pertain to the following case.

E.S., a previously well 5-year-old boy, presents to the emergency department (ED) with facial puffiness and severe periorbital edema. He has been receiving diphenhydramine for the past 2 days because his pediatrician prescribed it for a possible allergic reaction. However, his mother states that the diphenhydramine has not improved the swelling. He has no other symptoms, she says, but about 2 weeks ago he had a “bad cold.” His vital signs include temperature 37.3°C, heart rate 86 beats/minute, respiratory rate 21 breaths/minute, and blood pressure 96/58 mm Hg. He is alert and cooperative with the examination. His face shows moderate periorbital edema. His eyes are non-injected, his conjunctivas are not edematous, and his throat is not red. The dorsal surfaces of his hands and feet exhibit mild pitting edema. He has brisk capillary refill and 2+ pulses. Urinalysis shows 4+ protein and a specific gravity of 1.030. His chemistry panel is remarkable for protein 2 g/dL, serum albumin 1.4 g/dL, and cholesterol 350 mg/dL. Blood urea nitrogen (BUN) and creatinine values are normal. Twice-daily oral prednisone is started. He is followed as an outpatient clinically and with daily urine dipsticks. The edema and proteinuria gradually resolve with treatment over the next 8 weeks. The prednisone is tapered off, and he remains stable.

1. Which form of nephrotic syndrome is most accurately represented in E.S.?
 - A. Membranous nephropathy.
 - B. FSGS.
 - C. IgA nephropathy.
 - D. MCNS.
2. At a follow-up appointment 6 months later, E.S. is doing well. He has been off steroid therapy for 4 months and shown no signs of relapse. However, he has what appears to be a mild upper respiratory infection. E.S. is due for his 4- to 6-year-old vaccinations, including varicella. Because children with nephrotic syndrome are at increased risk of infection, a delay in vaccinations raises concerns. Which is the best time for E.S. to receive his varicella vaccine?
 - A. He may receive the vaccine today, because he has been off steroids for 1 month.
 - B. He may receive inactivated vaccines today but may not receive live vaccines because he is immunocompromised.
 - C. He may not receive the vaccine today, because he has an infection.
 - D. He may receive all of his vaccines, but they should be separated by several weeks to allow for maximal response.

Patient Cases (*continued*)

3. T.M. is a 12-year-old girl with FSGS that was diagnosed when she was 7 years old. She had been in remission for the previous 3 years, but about 6 months ago she had a severe disease recurrence that resulted in an episode of acute renal failure. Since then, she has been treated with high-dose prednisone 2 mg/kg/day and cyclosporine 2.5 mg/kg per dose by mouth twice daily. Her cyclosporine trough concentration in her laboratory tests at this appointment is 184 ng/mL. She is concerned about weight gain and insomnia. Her mother states that she eats healthily but notes that she has gained about 6.8 kg (15 lb) in the past 6 months. T.M. is being teased at school because of her weight gain and “moon face.” Which is the best solution to address this?
 - A. Discontinue cyclosporine therapy.
 - B. Begin a prednisone taper while monitoring carefully for symptom flare.
 - C. Suggest dietary modification, keeping fats to less than 30% of total caloric intake.
 - D. Switch cyclosporine to tacrolimus, which causes less weight gain.
4. A nurse from the outpatient infusion clinic calls you about T.S., a 10-year-old boy being treated in an outpatient infusion clinic who is scheduled to receive a rituximab infusion today. The nurse asks whether pretreatment is necessary and, if so, which regimen would be best to pretreat with:
 - A. Yes, pretreatment with methylprednisolone, acetaminophen, and diphenhydramine is recommended.
 - B. Yes, pretreatment with a saline fluid bolus, acetaminophen, and diphenhydramine is recommended.
 - C. No, pretreatment is unnecessary unless the child has had a reaction in the past.
 - D. No, pretreatment is unnecessary; infusion-related reactions to rituximab are rare.

III. HYDRONEPHROSIS**A. Pathophysiology**

1. This wide spectrum of disease processes includes transient dilation of the collecting system, upper or lower urinary tract obstructive uropathy, nonobstructive processes such as VUR, and prune belly syndrome.
2. Hydronephrosis can result from interruption by anatomic or functional processes of the flow of urine. This can occur anywhere along the urinary tract, from the kidneys to the urethral meatus. The rise in ureteral pressure leads to marked changes in glomerular filtration, tubular function, and renal blood flow. Glomerular filtration rate declines significantly within hours of acute obstruction and can persist for weeks after the obstruction is relieved. The ability to transport sodium, potassium, and hydrogen and to concentrate and to dilute the urine is severely impaired. The extent and persistence of these functional insults is directly related to the duration and extent of the obstruction. Chronic destruction can lead to profound tubular atrophy and permanent nephron loss.
3. In acute hydronephrosis, correction allows full recovery of renal function.
4. In chronic hydronephrosis, the loss of function is irreversible. The change from acute to chronic hydronephrosis can take as little as 6 weeks.

B. Epidemiology

1. Incidence is 2–9 per 1000 children.
2. Between 0.5% and 4.5% of all pregnancies annually are affected.
3. One of the most common findings on prenatal ultrasonography, its incidence is 1%–5%.

C. Diagnosis

1. Prenatal renal ultrasonography
2. Measurement of anterior-posterior diameter
3. Postnatal renal ultrasonography for infants with moderate to severe antenatal hydronephrosis. This is done between 48 hours of life and 2 weeks of age and repeated at 6–12 months.
4. Voiding cystourethrography in the first days of life is considered for all infants with prenatal hydronephrosis, particularly infants with postnatal ultrasonography revealing moderate to severe hydronephrosis.
5. Nuclear renography is performed in infants with high-grade hydronephrosis when underlying obstruction is suspected.
6. Serum and urinary biomarkers are an area of current study.

D. Grading

1. Traditional grading system – Very subjective
 - a. Mild
 - b. Moderate
 - c. Severe
2. Society for Fetal Urology (SFU) grade
 - a. Grade 0: No splitting
 - b. Grade I: Urine in pelvis barely splits sinus
 - c. Grade II: Urine fills intrarenal pelvis or urine fills extrarenal pelvis major calyces, dilated
 - d. Grade III: SFU grade II and minor calyces, uniformly dilated and parenchyma preserved
 - e. Grade IV: Grade III appearance plus thinned parenchyma
3. Anterior-posterior diameter
 - a. Anterior–posterior diameter greater than 15 mm represents severe or significant hydronephrosis.
 - b. A diameter of greater than 10 mm is the cutoff for significant hydronephrosis in the second trimester and greater than 15 mm in the third trimester.
 - c. Smaller diameters may reach significance if calyceal dilation is also present.

E. Etiology

1. Transient hydronephrosis
 - a. In most children with an antenatal history of dilation of the renal pelvis and calyces, transient hydronephrosis will resolve with no chronic issues. It can be related to ureteropelvic junction (UPJ) or natural folds that can occur early in development and resolve with maturity.
 - b. The incidence of transient hydronephrosis is 41%–88%.
2. UPJ obstruction
 - a. UPJ obstruction is usually suspected with pelvicaliceal dilation without ureteral dilation and is commonly unilateral.
 - b. The incidence in children is 5%–64%. Among children with antenatal hydronephrosis, 10%–30% will have UPJ obstruction.
 - c. Children with UPJ obstruction have an increased incidence of other urologic abnormalities.
3. VUR
 - a. VUR is suspected when there is a variable amount of hydronephrosis or hydroureteronephrosis.
 - b. There is currently no reliable way to diagnose VUR on fetal ultrasonography.
 - c. VUR occurs in 10%–20% of children with antenatal hydronephrosis.

F. Treatment

1. Infants with antenatal hydronephrosis are 12 times more likely to have pyelonephritis-related hospitalizations in the first year of life.
2. The risk of UTI increases with increasing grade of hydronephrosis and peaks at 40% in children with grade IV hydronephrosis (SFU scale).
3. Girls and uncircumcised boys with hydronephrosis appear to be at higher risk of UTI.
4. Antibiotic prophylaxis remains controversial. Epidemiologically focused studies have weakly recommended that children with mild hydronephrosis receive no prophylaxis, whereas children with more severe disease may benefit. Other studies have suggested that antibiotic prophylaxis is useful in all children with antenatal hydronephrosis. The risk of antibiotic resistance is often discussed but has not been well evaluated. No intervention at this time has been shown to reduce the incidence of renal scarring.
 - a. Several review articles mention amoxicillin 10 mg/kg/day as a possible prophylactic treatment option for UTI in patients with hydronephrosis or VUR. The recommendation is based on expert opinion because this option has not yet been prospectively evaluated for efficacy. Sulfamethoxazole/trimethoprim, nitrofurantoin, cephalexin, and trimethoprim have been evaluated in prospective studies and can also be used for prophylaxis.
 - b. In 2013, a meta-analysis of antibiotic prophylaxis in children with antenatal hydronephrosis (Pediatrics 2013;131:e251-e261) was conducted. Pooled UTI rates in patients with low-grade hydronephrosis were similar, regardless of whether the infants were undergoing continuous antibiotic prophylaxis (CAP). In children with high-grade hydronephrosis, patients receiving CAP had a significantly lower UTI rate than did those not receiving CAP (14.6% [95% CI, 9.3–22] vs. 28.9% [95% CI, 24.6–33.6], $p < 0.01$). The number needed to treat to prevent one UTI in patients with high-grade hydronephrosis was 7.
 - c. A 2014 pilot study of children 1–5 months of age with hydronephrosis or hydroureteronephrosis SFU grade III/IV was conducted (J Urol 2014;191(5 suppl):1501-7). Patients were given CAP with trimethoprim 2 mg/kg/day orally or matching placebo for 12 months or until the first febrile UTI (whichever came first). The authors found that UTI developed in 20.7% of patients. Because this was a pilot study, the authors did not power or design the study to capture efficacy differences between the treatment and placebo groups with regard to outcomes.
 - d. The results of the multiyear RIVUR (Randomized Intervention for Children with Vesicoureteral Reflux) were published in 2014. This was a 2-year multisite, randomized, placebo-controlled trial that included 607 children, 2–71 months of age, with a diagnosis of grade I–IV VUR after a first or second febrile or symptomatic UTI. Children were randomized to receive a daily sulfamethoxazole/trimethoprim suspension dosed at 3 mg trimethoprim/kg/day or a matching placebo. The median age of those enrolled was 12 months, and 558 (99.1%) of the participants were female. The risk of febrile or symptomatic recurrence was reduced by half among children who received prophylaxis compared with those who received placebo, and the difference widened over time (hazard ratio [HR], 0.50; 95% CI, 0.34–0.74). The authors found that eight children (95% CI, 5–16) would have had to be treated for 2 years to prevent one case of febrile or symptomatic UTI. The impact on renal scarring was evaluated, and outcome scans revealed no significant difference between groups in the incidence of renal scarring (11.9% in the prophylaxis group and 10.2% in the placebo group, $p = 0.55$). Among 87 children with a first febrile or symptomatic recurrence with *E. coli*, the proportion of isolates resistant to sulfamethoxazole/trimethoprim was 63%, compared with 19% in the placebo group. The authors stated that their data supported reduced recurrence in treated children and suggested that decision analysis and cost-effectiveness analysis could further clarify the role of antimicrobial prophylaxis in the future.

- e. A recent trial in Thailand (Investig Clin Urol 2020;61:200-6) evaluated CAP for prevention of UTI in infants with mild to moderate isolated antenatal hydronephrosis (SFU grade less than 4). Eighty neonates, 7–30 days of age, were randomly assigned to either (1) the CAP arm, which received cephalexin 10–15 mg/kg/day until patients were 3 months of age, which was then changed to sulfamethoxazole/trimethoprim 2–3 mg/kg/day until hydronephrosis resolution or patients were 12 months of age; or (2) an observation arm. The primary outcome was UTI. The study was terminated early because of the higher probability of UTI noted in the CAP arm (HR 1.38; 95% CI, 0.37–5.16; $p=0.63$) and a 4-fold increase in sulfamethoxazole/trimethoprim-resistant bacteria in the CAP group. The authors concluded that the benefit of CAP in mild to moderate hydronephrosis was unclear and that CAP increased the risk of resistant bacterial organisms.

Patient Case

5. A urologist is consulting on a newborn in the neonatal ICU that you cover. The infant is a 2-month-old born at 38 weeks' gestation. The infant was noted to have antenatal hydronephrosis, and ultrasonography today reveals grade IV hydronephrosis. The nephrologist would like a recommendation for an antibiotic. Which recommendation do you believe is best?
 - A. Give sulfamethoxazole/trimethoprim, 3 mg trimethoprim/kg/day.
 - B. Give amoxicillin 30 mg/kg/day.
 - C. Currently the risk of antibiotic therapy in a newborn outweighs the benefit.
 - D. CAP is not recommended, because of the risk of antibiotic resistance.

IV. RENAL TUBULAR ACIDOSIS

A. Acid-Base Homeostasis

1. The nephron regulates acid–base balance by regulating bicarbonate reabsorption and hydrogen ion secretion. When blood at pH 7.4 enters the glomerular capillaries, hydrogen, bicarbonate, sodium, and potassium are filtered and enter the proximal tubular lumen. The proximal tubule reclaims the filtered base (about 85% of total). Failure to reabsorb the base results in metabolic acidosis. Normally, there is net reabsorption in the proximal tubule of sodium and bicarbonate, with no change in luminal pH. Urine passes through the lumen and exits the loop of Henle at pH 7.4 before entering the distal tubule. The distal tubule secretes hydrogen ion and generates a hydrogen gradient. The distal tubule will directly secrete hydrogen into the tubular lumen independent of sodium, using the H^+ -ATPase pump. The distal tubule also generates ammonia. This will cause the urine pH to change to 4.5–8.
2. In types 1 and 2 RTA (renal tubular acidosis), there is impaired bicarbonate reabsorption in the proximal tubule, impaired hydrogen ion excretion in the distal tubule, or both.
3. In type 4 RTA, there is aldosterone deficiency or aldosterone resistance, resulting in inability to excrete hydrogen and potassium ions. Retention of these ions causes metabolic acidosis and hyperkalemia.

B. Epidemiology

1. No epidemiologic studies are available, but overall incidence is said to be “low” by most references.
2. Children typically present with primary RTA caused by inherited genetic defects in tubular proteins versus adults, in whom RTA is usually a result of acquired causes.
3. Relative incidence in children is based on RTA type: type 1 > type 4 > type 2.

C. Diagnosis (see Table 1)

1. Hyperchloremic metabolic acidosis
2. Normal plasma anion gap $[\text{Sodium}] - ([\text{Bicarbonate}] + [\text{Chloride}])$
3. Negative urinary anion gap $(\text{Urine } [\text{Na}^+] + \text{Urine } [\text{K}^+] - \text{Urine } [\text{Cl}^-])$
4. Urine pH and blood pCO_2
5. Serum electrolytes
6. Patient symptomology
7. Medication (medications such as carbonic anhydrase inhibitors, electrolytes, amphotericin B, ifosfamide, cisplatin, sodium valproate, aminoglycosides, expired tetracycline (via anhydro-4-epitetracycline), and cholestyramine can alter acid-base balance)

Table 1. Characteristics of Renal Tubular Acidosis

Finding	Type 1: Distal RTA	Type 2: Proximal RTA	Type 4 RTA
Primary characteristic	Decreased distal acidification	Decreased proximal bicarbonate reabsorption	Aldosterone deficiency or resistance
Plasma bicarbonate	$\leq 10 \text{ mEq/L}$	$12\text{--}20 \text{ mEq/L}$	$\geq 15 \text{ mEq/L}$
Urine pH	> 5.5	Variable	< 5.5
Serum potassium	Low	Low	High
Urine anion gap	Positive	Negative	Positive
GFR	Normal	Normal	Low
Nephrocalcinosis	Yes	No	No

D. Types and Pathophysiology

1. Type 1, “distal RTA”
 - a. Because base reabsorption is handled primarily by the proximal tubule, the distal tubule is responsible for formation of a hydrogen ion gradient between the blood and tubular lumen by which to regulate blood pH.
 - b. Distal RTA may be caused by disease states, including sickle cell anemia, Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus, hyperparathyroidism, hyperthyroidism, chronic hepatitis, primary biliary cirrhosis, rejection of a transplanted kidney, renal medullary cystic disease, obstructive uropathy, and chronic urinary tract infections.
 - c. Distal RTA may also be caused by medications, including amphotericin B, cyclophosphamide, foscarnet, ifosfamide, and lithium.
 - d. In distal RTA, distal urinary hydrogen ion secretion is impaired; this can be caused by impaired function of transporters or proteins involved in the acidification process, including the H^+ -ATPase pump, bicarbonate/chloride anion exchangers, or components of the aldosterone pathway.
 - e. Because of this impaired hydrogen ion excretion, urine pH cannot be reduced below 5.5, despite severe metabolic acidosis.
 - f. The outcome is a loss of sodium bicarbonate, resulting in hyperchloremia and hypokalemia. Hypercalciuria can be present, leading to nephrocalcinosis (excessive calcium deposition in the kidneys) or nephrolithiasis.
 - g. Chronic acidosis can also lead to urinary citrate excretion, which exacerbates calcium deposition in the tubules.
 - h. Mobilization of organic components from bone to serve as buffers for chronic acidosis, combined with hypocalcemia, can lead to severe bone disease.
 - i. Patients with distal RTA present with growth failure and metabolic acidosis.

2. Type 2, “proximal RTA”
 - a. Type 2 RTA is characterized by an impairment in proximal bicarbonate reabsorption resulting in a hypokalemic hyperchloremic metabolic acidosis. There are both inherited and acquired forms. Proximal RTA usually occurs as part of more global proximal tubular dysfunction or Fanconi syndrome (low-molecular-weight proteinemia, glycosuria, phosphaturia, aminoaciduria, and proximal RTA).
 - b. Hereditary causes include cystinosis, galactosemia, tyrosinemia, glycogen storage disease type 1, and Wilson disease.
 - c. Acquired disorders include hypocalcemia and vitamin D deficiency and drugs or toxins. Some drug causes include acetazolamide, aminoglycosides, cisplatin, ifosfamide, streptozocin, valproic acid, and outdated tetracycline. Toxin causes include both lead and mercury. Amyloidosis and renal transplant rejection can also cause type 2 proximal RTA.
 - d. The inability of the proximal tubule to achieve net hydrogen elimination results in a non-anion gap metabolic acidosis. There is a resulting loss of potassium and some sodium. The sodium loss provokes volume contraction and release of aldosterone, which exacerbates the potassium loss, causing significant hypokalemia.
 - e. Urinalysis findings are normal. The urine pH is acidic (less than 5.5) if plasma bicarbonate stores are already depleted. Urine pH may be greater than 7 before this occurs. This is why urine pH is denoted as variable in Table 1. In patients with long-term type 2 RTA, there may be alternations in SCr and GFR.
 - f. Patients with type 2 RTA present with growth failure in the first year of life and may have polyuria, dehydration, anorexia, vomiting, constipation, osteopenia, and hypotonia.
 3. Type 4, “hyperkalemic RTA”
 - a. If aldosterone production is impaired (hypoaldosteronism) or the kidneys do not respond to aldosterone normally (“pseudo” hypoaldosteronism), type 4 RTA will occur. Aldosterone has direct effects on the H^+ -ATPase; therefore, without aldosterone, acidosis results. Aldosterone is also a stimulant for potassium secretion in the collecting tubule, and in its absence, hyperkalemia will result.
 - b. In children, aldosterone unresponsiveness is more common than hypoaldosteronism. This may occur transiently because of acute pyelonephritis or acute urinary obstruction. It may also occur chronically in infants and children with obstructive uropathy. Inherited type 4 RTA is reported but very rare.
 - c. Drugs that may cause type 4 RTA include ACEIs/ARBs, heparin, K^+ -sparing diuretics, NSAIDs, pentamidine, and trimethoprim.
 - d. Children with type 4 RTA present with growth failure, polyuria, and dehydration. Life-threatening hyperkalemia is uncommon.
 - e. A hyperkalemic non-gap metabolic acidosis is present. Urine pH is usually less than 5.5 when acidosis is present. Urine sodium concentration is high, but urine potassium is low, reflecting the absence of aldosterone effect.
- E. Treatment (see Table 2): Treatment is based on the type of RTA, but bicarbonate therapy is the mainstay for all forms. Patients with RTA can require up to 20 mEq/kg/day of bicarbonate in the form of sodium bicarbonate or sodium citrate solution. The overall treatment approach varies slightly with the specific RTA type. Removal of any drug-induced cause of RTA is an area in which the pharmacist can play a critical role. Correction of underlying acidosis has been associated with improved growth and bone mineral density in children with RTA.
1. Type 1 distal RTA: Sodium bicarbonate, sodium citrate, or potassium citrate 2–10 mEq/kg/day. The dose varies widely, with younger children typically requiring higher doses than older children and adolescents. Younger children may require larger doses because of their naturally higher urine pH and the acid load caused by rapid skeletal bone growth.

- a. Treatment with citrate may be preferred to bicarbonate because citrate supplementation can increase urinary excretion of citrate, reducing the risk of calcium oxalate stone formation. The risk is that high urinary citrate may also increase urine pH and raise the risk of calcium phosphate stone formation.
 - b. Potassium citrate is often preferred to sodium citrate because hypercalciuria can be induced by increased sodium intake that inhibits calcium reabsorption in the proximal tubule.
 - c. A study evaluating the optimal dose of potassium citrate in type 1 distal RTA found that a 4-mEq/kg/day dose of potassium citrate corrected the urinary abnormalities and minimized the risk of calcium oxalate stones (Am J Kidney Dis 2002;39:383-91). The authors suggested that all children be monitored for urinary calcium/creatinine ratio or citrate/creatinine ratio to ensure adequate potassium citrate supplementation.
 - d. Monitor for hypercalciuria and treat with hydrochlorothiazide 1–3 mg/kg/day in divided doses twice daily if it develops. Thiazide diuretics reduce urinary calcium excretion by inducing extracellular volume depletion, which in turn causes increased renal sodium and calcium reabsorption by directly increasing distal calcium reabsorption. An additional benefit of thiazide diuretics is that their long-term use is associated with preservation of bone mineral density.
2. Type 2 proximal RTA: Sodium bicarbonate, sodium citrate, or potassium citrate 5–15 mEq/kg/day. A combination of sodium- and potassium-based alkalinization may be required for balance.
 - a. Correction of metabolic acidosis in proximal RTA typically requires higher doses of alkalinization than those used in distal RTA; raising the serum bicarbonate concentration increases the filtered bicarbonate load above the proximal tubule's reduced reabsorptive capacity, resulting in a marked bicarbonate diuresis.
 - b. If RTA is associated with Fanconi syndrome, phosphate supplementation may be required as well. Calcium and vitamin D supplementation may also be required for prevention of osteopenia.
 3. Type 4 RTA: Treatment of acidosis as above, but preference should be toward sodium-based alkalinization because of underlying hyperkalemia
 - a. If hyperkalemia persists, many children are treated with sodium polystyrene sulfonate. Infant studies have shown successful treatment of hyperkalemia with pretreatment of infant formula with sodium polystyrene sulfonate. This can result in a dramatic increase in sodium in the formula, which must be monitored. To further address hyperkalemia, children may be treated with a loop diuretic such as furosemide 1–2 mg/kg/day. If nephrocalcinosis or osteopenia is a problem, a thiazide such as hydrochlorothiazide 1–3 mg/kg/day could be considered.
 - b. A final option is treatment with fludrocortisone 0.05–0.15 mg/m²/day (typical max of 0.3 mg/day). This is particularly useful in children with suspected underlying congenital adrenal hyperplasia.

Table 2. Urinary Alkalinizers

Drug	Dosage Form	Pediatric Pharmacist Tips
Potassium citrate and citric acid: Cytra-K Crystals 2 mEq/mL Cytra-K Solution 2 mEq/mL Potassium citrate: Urocit-K extended-release tablets (5 mEq, 10 mEq, 15 mEq)	Powder packet termed <i>crystals</i> : Each packet contains potassium 30 mEq and bicarbonate 30 mEq. Solution: Each milliliter contains 2 mEq of potassium and 2 mEq of bicarbonate equivalent Tablets: Available in extended release at dosages of 5, 10, and 15 mEq	Powder packets: The manufacturer suggests mixing one packet in at least 180 mL of water, yielding a final concentration 0.167 mEq/mL, making milliliter dosage quite difficult for a child. Many mix in 15 mL of water instead to make a 2-mEq/mL solution if the child can tolerate it. Fruit punch flavor when mixed in solution No stability information or storage recommendation for the powder once it is mixed in solution Solution: Manufacturer suggests diluting doses with “½ glass of water” Citrus/berry flavor Contains propylene glycol, sodium benzoate, and sorbitol Tablets: About 1 inch long and may not be crushed or chewed

Table 2. Urinary Alkalinizers (*continued*)

Drug	Dosage Form	Pediatric Pharmacist Tips
Sodium bicarbonate: 1-mEq/mL injection solution 325-mg (3.8 mEq) or 650-mg (7.7 mEq) tablets Baking soda powder (26.8 mEq bicarbonate per ½ teaspoon)	Can be made with 8.4% (1 mEq per mL) IV product given orally or with sodium bicarbonate powder and sterile water	Bitter salty taste: Recommend flavoring for palatability, especially because the doses on a volume basis can be large in older children. Citrus flavors tend to mask best If the child is old enough, can consider using sodium bicarbonate tablets to avoid taste issues, though the pill burden may be significant Some centers will instruct parents to use baking soda; brand name Arm & Hammer tastes slightly better, but most children will not find this palatable unless well hidden in soft food
Sodium citrate and citric acid: Bicitra Cytra-2 Oracit Shohl solution (modified)	Solution Each milliliter contains 1 mEq of Na ⁺ and 1 mEq of bicarbonate	For all products: Manufacturers suggest diluting in 1–3 oz of water Refrigeration may improve taste Cytra-2 is grape flavor. Contains propylene glycol, sodium benzoate, and sorbitol Oracit contains no flavoring. Contains methyl- and propyl-parabens Shohl solution is a compounded product that may contain alcohol; if desired, flavoring can be added to enhance taste
Potassium citrate, sodium citrate, and citric acid: Cytra-3 Tricitrates SF	Solution/syrup Each milliliter contains potassium 1 mEq, sodium 1 mEq, and bicarbonate 2 mEq	All manufacturers recommend further dilution before administration Cytra-3 is raspberry flavored and sugar free syrup (contains saccharin) Tricitrates is raspberry flavored and sugar free solution (contains sorbitol)
Potassium bicarbonate and Citric acid: Effer-K (10 mEq, 20 mEq, and 25 mEq)	Effervescent tablets for solution	Manufacturer recommends dissolving in at least 4 oz of water or juice The 10-mEq tablets are available in cherry vanilla or unflavored The 20-mEq tablets are available in orange cream or unflavored All tablets contain dextrose but unflavored do not contain dyes

IV = intravenous.

Patient Cases

6. A 5-year-old girl (weight 13 kg) presents with failure to thrive. She has no history of diarrhea or vomiting. Serum electrolyte values are sodium 136 mEq/L, chloride 111 mEq/L, and bicarbonate 13 mEq/L. Urine electrolyte values are sodium 30 mEq/L, chloride 40 mEq/L, and potassium 20 mEq/L. Urine pH is 6.5. Which figure best depicts the plasma anion gap?
- A. 12 mEq/L.
 - B. 24 mEq/L.
 - C. 8 mEq/L.
 - D. 13 mEq/L.
7. C.J. is a 12-day-old girl (weight 3.2 kg) admitted to the ED with severe dehydration, vomiting, jaundice, and failure to thrive. Her urine pH is 5.0, serum sodium 130 mEq/L, potassium 6.4 mEq/L, and bicarbonate 18 mEq/L. Her SCr is 0.6 mg/dL. The ED physician administers intravenous fluids and gives intravenous sodium bicarbonate, with minimal resolution of her acid–base imbalance. Hypoaldosteronism is suspected, with type 4 RTA. Which is the best treatment for the physician to give next in an effort to combat the persistent hyperkalemia?
- A. Dietary potassium restriction.
 - B. Furosemide 1 mg/kg per dose intravenously.
 - C. Normal saline bolus 10 mL/kg over 1 hour.
 - D. Spironolactone 2 mg/kg by mouth once daily.

V. ACUTE KIDNEY INJURY (ACUTE RENAL FAILURE)**A. Definitions and Background**

1. Acute kidney injury (AKI) is defined as an acute decrease in kidney function.
2. Neonatal AKI is distinct from AKI in infants and older children.
 - a. Nephrogenesis begins at the fifth week of gestation and continues until 34–36 weeks' gestation. Renal blood flow is naturally lower in newborn kidneys than in the kidneys of older children or adults. GFR in healthy full-term infants is 10–20 mL/minute/1.73 m² and increases to 30–40 mL/minute/1.73 m² in the first 2 weeks of life. In preterm infants, GFR at birth is lower and increases more slowly. Tubular function is also immature in preterm infants, and their ability to resorb electrolyte and protein and concentrate urine is impaired.
 - b. AKI in the newborn cannot be defined by oliguria, because neonates commonly have AKI without urine output less than 0.5 mL/kg/hour (non-oliguric renal failure).
 - c. SCr is also a nonspecific indicator in the neonate; after birth, the neonatal SCr reflects maternal concentrations, which will decline over days to weeks.
 - i. A 1999 study proposed that in neonates, creatinine concentration rises significantly in the first 48 hours of life (Pediatrics 1999;104:e76). This is notable, particularly in infants born at less than 30 weeks' gestation. The authors concluded that rising SCr in the first 48 hours of life should not be used alone to diagnose AKI in the newborn.
 - ii. SCr is a marker of kidney function, not damage. Concentrations may not change until 25%–50% of kidney function has already been lost, and at a lower GFR, SCr will overestimate renal function because of the tubular secretion of creatinine.

- iii. Other studies have noted that measurement of SCr in the neonate is less often obtained because of concerns about blood loss from several samplings and that AKI may therefore go undetected for prolonged periods.
- d. A National Institute of Diabetes and Digestive and Kidney Diseases workshop panel of neonatologist and nephrologists has proposed a modification of the KDIGO criteria for AKI specific to neonates and for use in children younger than 120 days to define AKI for research and consistency purposes. See Table 3.

Table 3. Neonatal AKI KDIGO Classification

Stage	SCr	Urine Output
0	No change in SCr or rise < 0.3 mg/dL	≥ 0.5 mL/kg/hr
1	SCr rise ≥ 0.3 mg/dL within 48 hr or SCr rise ≥ 1.5–1.9 × reference ^a SCr within 7 days	< 0.5 mL/kg/hr for 6–12 hr
2	SCr rise ≥ 2.0–2.9 × reference SCr ^b	< 0.5 mL/kg/hr for ≥ 12 hr
3	SCr rise ≥ 3 × reference SCr or SCr ≥ 2.5 mg/dL ^b or receipt of dialysis	< 0.3 mL/kg/hr for ≥ 24 hr or anuria for ≥ 12 hr

^aReference SCr is the lowest previous SCr.

^bSCr value of 2.5 mg/dL represents < 10 mL/min/1.73 m².

- e. The AWAKEN (Assessment of Worldwide Acute Kidney Injury and Epidemiology in Neonates) study group, which is a part of the Neonatal Kidney Collaborative (NKC), recently published the results of a multicenter, multinational retrospective cohort study that looked at critically ill neonates admitted to neonatal intensive care units to identify the incidence of AKI and its association with mortality and length of hospital stay (Lancet Child Adolesc Health 2017;1: 184-94). In this study the authors used a modified AKI definition, with the original KDIGO tool as the basis. This is a re-engineering of the group's previously published modified tool (see Table 3). In this new version of the tool, the UOP increments have been removed and they have slightly modified the UOP definitions. It remains to be seen which tool will be accepted as the gold standard for defining neonatal AKI. See Table 4.

Table 4. Neonatal AKI AWAKEN Classification

Stage	SCr	Urine Output
0	No change in SCr or increase < 0.3 mg/dL	≥ 1 mL/kg/hr
1	SCr rise ≥ 0.3 mg/dL within 48 hr or SCr rise ≥ 1.5–1.9 × reference ^a SCr within 7 days	> 0.5 mL/kg/hr and ≤ 1 mL/kg/hr
2	SCr rise ≥ 2.0–2.9 × reference SCr	> 0.3 mL/kg/hr and ≤ 0.5 mL/kg/hr
3	SCr rise ≥ 3 × reference SCr or SCr ≥ 2.5 mg/dL or receipt of dialysis	≤ 0.3 mL/kg/hr

^aReference SCr is the lowest prior SCr measurement.

- f. Serum and urine biomarkers may help identify AKI in neonates more readily.
 - i. Cystatin C: A low-molecular-weight protein that is independent of muscle mass and freely filtered by the glomerulus and totally metabolized by the renal tubule. Cystatin C can distinguish neonate renal function from maternal, even in the first 5 days of life. It is a serum biomarker. Several cystatin-C-based GFR formulas currently exist and it continues to gain momentum and support for widespread use in both adult and pediatric patients (Pharmacy 2020;8: 35-53).

- ii. Neutrophil gelatinase–associated lipocalin (NGAL): NGAL is a ubiquitous protein bound to gelatinase from human neutrophils. NGAL expression increases in the presence of inflammation and injured epithelium and is one of the earliest proteins induced in the kidney after ischemic or toxic insult. NGAL monitoring is noninvasive because it can be detected in the urine. NGAL has not yet found a role in bedside diagnosis and management of AKI, but it is being widely studied. It is a urinary biomarker.
 - iii. Kidney injury molecule-1 (KIM-1): KIM-1 is a type I transmembrane glycoprotein that is undetectable in healthy kidneys. During kidney injury, there are very high levels on the apical membrane of proximal tubule cells that can then be detected in the urine. KIM-1 may also be an appropriate noninvasive marker of chronic kidney damage. Like NGAL, however, it is not yet used widely in clinical practice. It is a urinary biomarker.
3. Pediatric AKI – No universally accepted definition. Two classification systems have emerged for AKI and are in wide use. There are also many equations for estimating GFR in children.
 - a. pRIFLE: Pediatric **R**isk of renal dysfunction, **I**njury to the kidney, **F**ailure of kidney function, **L**oss of kidney function, and **E**nd-stage renal disease. Modified pediatric version of the adult criteria. Uses change in CrCl as estimated with the Schwartz formula, in addition to urine output in milliliters per kilogram per hour, to estimate risk.
 - b. Acute Kidney Injury Network (AKIN) criteria: According to time in relation to absolute creatinine increase, percentage increase, or documented oliguria. The AKIN criteria broaden the time window for AKI diagnosis. The AKIN criteria have not been as widely studied in pediatric patients, but they can be found in the more recent literature evaluating AKI in children.
 - c. The Schwartz equation has been the most commonly accepted standard in pediatric patients for estimating CrCl. This formula should not be used with SCr measurements calibrated to reference measurements by isotope dilution mass spectrometry (IDMS). Using IDMS creatinine values in the traditional Schwartz equation will result in an overestimation of GFR by 18%–39%, depending on the patient’s age. The overestimation is highest in children younger than 3 years. The traditional Schwartz equation is:

$$\text{CrCl (milliliters/minute/1.73 m}^2\text{)} = K \times L/\text{SCr}$$

where K is the constant of proportionality that is age-specific, L is length in centimeters, and SCr is serum creatinine concentration in milligrams per deciliter.

Age	K
Preterm ≤ 1 yr	0.33
Full-term ≤ 1 yr	0.45
1–13 yr	0.55
13–18-yr female	0.55
13–18-yr male	0.7

- d. The *modified* Schwartz equation: In 2009, the equation was updated to account for more modern creatinine calculations done by laboratories. Instead of a variable K value, the modified Schwartz uses a set K of 0.413 with length in centimeters and SCr in milligrams per deciliter, using IDMS values or equivalent. Also called the *bedside* Schwartz equation.

$$\text{CrCl (milliliters/minute/1.73 m}^2\text{)} = 0.413 \times L/\text{SCr}$$

4. Adult AKI – Definitions still vary. Sometimes these are broadly used to include children as well.
 - a. One definition is to use an increase in SCr of 0.5 mg/dL or greater or an increase of 1 mg/dL or greater in SCr in patients with preexisting CKD. Some studies also suggest a decrease of 25% or greater in the GFR of a patient with CKD.
 - b. AKI in adults may also be defined by urine output.
 - i. Anuric: Less than 50 mL of urine output in 24 hours
 - ii. Oliguric: Urine output of 50–500 mL in 24 hours
 - iii. Nonoliguric: More than 500 mL in a 24-hour period
 - c. RIFLE criteria: Similar to pRIFLE criteria but with more emphasis on the use of SCr as a marker
 - d. AKIN criteria: Less emphasis on CKD in staging

Table 5. Criteria for Use in Diagnosis of Acute Kidney Injury

Scheme	Stage	Creatinine Criteria	Urine Output Criteria
RIFLE	R	$\uparrow \geq 1.5\times$ or $\downarrow$ GFR $\geq 25\%$	< 0.5 mL/kg/hr for 6 hr
	I	$\uparrow \geq 2\times$ or $\downarrow$ GFR $\geq 50\%$	< 0.5 mL/kg/hr for 12 hr
	F	$\uparrow \geq 3\times$ or SCr > 350 mm ³ /L (~3.96 mg/dL)	< 0.3 mL/kg/hr for 24 hr or anuria for 12 hr
	L	Persistent failure > 4 wk	
	E	Persistent failure > 3 mo	
Pediatric RIFLE	R	$\downarrow$ Estimated CrCl by $\geq 25\%$	< 0.5 mL/kg/hr for 8 hr
	I	$\downarrow$ Estimated CrCl by $\geq 50\%$	< 0.5 mL/kg/hr for 16 hr
	F	$\downarrow$ Estimated CrCl by $\geq 75\%$ or estimated CrCl < 35 mL/min/1.73 m ²	< 0.3 mL/kg/hr for 24 hr or anuria for 12 hr
	L	Persistent failure > 4 wk	
	E	Persistent failure > 3 mo	
AKIN	1	$\uparrow$ in SCr ≥ 0.3 mg/dL or $\uparrow$ in SCr to 150%–200% baseline	< 0.5 mL/kg/hr for 6 hr
	2	$\uparrow$ to 200%–300% baseline SCr	< 0.5 mL/kg/hr for 12 hr
	3	$\uparrow$ in SCr to $\geq 300\%$ baseline or ≥ 4 mg/dL SCr with an acute $\uparrow$ of 0.5 mg/dL	< 0.3 mL/kg/hr for 24 hr or anuria for 12 hr

B. Epidemiology

1. It is difficult to state epidemiology statistics because of the variable definitions of AKI in neonates and children, combined with the lack of available research in pediatric age groups.
2. Large variances exist in reporting between developed and developing countries.
3. It is believed that critically ill neonates are more susceptible than older children and adults to AKI.
4. AKI incidence in critically ill newborns is 8%–24%, with mortality rates of 10%–61%.
5. The pediatric incidence has been 4.5%–82%, depending on the criteria used and the originating country of the study.

C. Risk Factors

1. Volume depletion – Vomiting, diarrhea, decreased fluid intake, fever, diuretic or NSAID use, and relative volume depletion, such as that in heart failure or nephrotic syndrome
2. Underlying CKD

3. Nephrotoxic medications – The most common offenders are listed below.
 - a. Amphotericin B
 - b. Aminoglycosides
 - c. ACEIs
 - d. ARBs
 - e. Calcineurin inhibitors
 - f. Chemotherapeutic agents (platins, ifosfamide, cytarabine, methotrexate, etc.)
 - g. Contrast dye (high molecular weight > low molecular weight)
 - h. NSAIDs
 - i. Piperacillin-tazobactam
 - j. Vancomycin
4. Obstruction of the urinary tract

D. Classifications of AKI

1. Prerenal – Result of either volume contraction or decreased effective blood volume
 - a. Hypoperfusion of the kidney
 - i. Hypovolemia (GI losses, congenital heart disease, sepsis)
 - ii. Increased urinary loss of fluids (osmotic diuresis, diabetes insipidus, diuretic use)
 - iii. Blood loss (trauma, hemophilia, surgical loss)
 - iv. Redistribution of extracellular fluid (liver disease, nephrotic syndrome, hypoalbuminemia)
 - v. Vasodilation (sepsis, anaphylaxis)
 - vi. Skin loss of fluids (burns, peritonitis, pancreatitis, cystic fibrosis, third space fluid loss)
 - b. Decreased perfusion leads to ischemic or toxic injury to renal cells and decrease in GFR. Compensatory mechanisms lead to decreased renal vascular resistance, decreased renal perfusion, and vasoconstriction.
 - c. Infants are at an increased risk of prerenal AKI because of the immature kidney's inability to concentrate urine, their large body surface area in relation to body mass, which can lead to high insensitve water losses, and their inability to communicate thirst.
 - d. Diagnosis is based on clinical history, decreased urine output, increased urine osmolarity (greater than 350 mOsm in neonates, greater than 400 mOsm in older children), low urinary sodium (less than 10 mEq/L), low fractional excretion of sodium (less than 2.5% neonates, less than 1% in older children), and increased BUN/SCr ratio. Renal ultrasonography and renal scan should appear normal.
2. Intrinsic renal disease
 - a. Parenchymal injury caused by vascular spasm, intravascular coagulation, and microvascular injury. Injury leads to cell breakdown and necrosis.
 - i. Acute tubular necrosis
 - ii. Interstitial nephritis
 - iii. HUS
 - iv. Glomerulonephritis
 - v. Nephrotoxic drugs
 - b. Diagnosis is based on clinical history, oliguria (urine output less than 0.5 mL/kg/hour child or less than 1 mL/kg/hour infant), or anuria; urine specimen may have red blood cell (RBC) casts or granular casts. Streptococcal antibodies, hepatitis B and C panels, and complements are also suggested as part of the workup. Urine osmolarity will be low (less than 350 mOsm) with a high urinary fraction of sodium (greater than 2% in older children, greater than 2.5%–3% in newborns). Renal scans and biopsy may further clarify the type of injury and its location within the kidney.

3. Postrenal
 - a. Obstruction of urine flow, including renal calculi, bladder outlet obstruction, and ureteral compression. These obstructions lead to an increase in fluid pressure near the obstruction, which can cause renal damage and decreased renal function.
 - b. Diagnosis is based on signs and symptoms of obstruction (hematuria, colicky pain). A history of antenatal hydronephrosis warrants a further workup. The physical examination will reveal flank pain and a flank mass if there is a UPJ obstruction. Urine output and urinary sediment findings can vary. Renal scan and ultrasonography will reveal a dilated renal pelvis.
- E. Prevention of AKI
 1. Ensure adequate intravascular volume status.
 2. Avoid nephrotoxic medications when possible.
 3. Enhanced monitoring of at-risk populations—for example, children with congenital heart disease, children with liver disease, children with underlying CKD, and children after bone marrow transplantation
 4. Careful and judicious use of contrast agents
 5. Parent education regarding fluid requirements during GI or febrile illness
- F. Management of AKI
 1. No consensus exists regarding the “right” balance of hydration, diuresis, and dialysis to manage AKI in infants/children. The management is heterogeneous and based on the disease process being treated.
 - a. Maintenance of renal perfusion
 - b. Use of renal vasodilators such as low-dose dopamine or fenoldopam has not been shown to improve AKI outcomes in children.
 - c. Vasoactive agents should be used after volume replacement as needed to maintain cardiac output and renal perfusion pressure.
 2. Fluid management
 - a. Will depend on the patient’s hemodynamic status and urine output
 - b. 10–20 mL/kg of isotonic fluid bolus or albumin/packed RBCs, if they are indicated, with repeat boluses as needed, depending on blood pressure, heart rate, capillary refill, and urine output
 - i. The SAFE trial of adult patients showed no survival difference between patients resuscitated with normal saline and those resuscitated with albumin.
 - ii. The updated Surviving Sepsis Campaign guidelines in 2020 now state that crystalloids are preferred to albumin for initial fluid resuscitation. However, the evidence is graded as weak; therefore, it is hoped that prospective trials will be conducted (Pediatr Crit Care Med 2020;21:e52-e106).
 - c. Once intravascular volume is replaced, daily maintenance needs must be reassessed. The clinician must account for insensible water losses and excretory water losses.
 3. Diuretics
 - a. Reducing fluid overload with diuretics can decrease the need for CRRT, but this has not been shown to improve AKI outcomes.
 - b. The half-life of loop diuretics in neonates and premature infants is significantly longer than in older children and adults.
 - c. Studies of furosemide in infants after congenital heart surgery have shown the possibility of lowering the daily dose received and obtaining fewer fluctuations in hemodynamics when furosemide is given in a continuous infusion rather than an intermittent infusion.
 4. Correction of electrolyte disturbances and acidosis
 - a. These are supportive and should be carefully done in the setting of AKI.
 - b. If they cannot be corrected, renal replacement therapy should be initiated.

5. Renal replacement therapy
 - a. Includes PD, intermittent hemodialysis (HD), and CRRT. The correct modality for a particular situation is still an area of speculation, though the overall use of renal replacement therapy in children is increasing.
 - b. Indications
 - i. Oliguria/anuria
 - ii. Hyperkalemia
 - iii. Severe metabolic acidosis
 - iv. Azotemia
 - v. Clinically significant organ edema (especially pulmonary)
 - vi. Uremic encephalopathy, pericarditis, or neuropathy/myopathy
 - vii. Drug overdose with dialyzable toxin
 - viii. Inborn errors of metabolism
6. New pharmacologic targets to treat or prevent AKI are under investigation.

Patient Case

8. You are rounding in the neonatal ICU with your pharmacy student on a neonate born at 32 weeks' gestation (weight 1.9 kg) who has just been admitted for respiratory distress. The student notes that the infant's SCr is 1.3 mg/dL, and the urine output in the 4 hours since delivery is 0.6 mL/kg/hour. Which assessment would best help define this infant's renal function?
 - A. AKIN.
 - B. RIFLE.
 - C. BUN.
 - D. Serum cystatin C.

VI. CHRONIC KIDNEY DISEASE

- A. Definitions and Background – CKD in children has been defined by the National Kidney Foundation according to the presence or absence of markers of kidney damage and the level of kidney function (GFR), irrespective of the type of kidney disease. The two independent criteria for CKD are:
 1. Kidney damage for 3 months or longer as defined by structural or functional abnormalities of the kidney with or without decreased GFR, manifesting as either pathologic abnormalities or markers of kidney damage, including abnormalities in the composition of the blood, urine, or abnormalities in imaging studies
 2. GFR less than 60 mL/minute/1.73 m² for 3 months or longer with or without kidney damage
- B. Classification
 1. Stage 1: Kidney damage with a normal or increased GFR (greater than 90 mL/minute/1.73 m²)
 2. Stage 2: Mild reduction in GFR (60–89 mL/minute/1.73 m²)
 3. Stage 3: Moderate reduction in GFR (30–59 mL/minute/1.73 m²)
 4. Stage 4: Severe reduction in GFR (15–29 mL/minute/1.73 m²)
 5. Stage 5: Kidney failure GFR (less than 15 mL/minute/1.73 m²)
- C. Epidemiology
 1. The 2018 National Health Interview Survey found that 6 million adults 18 years of age and over have kidney disease.

2. The prevalence of CKD in children is unknown but is estimated at 82 cases per million per year.
 3. African Americans and Latinos are disproportionately affected by CKD, partly because of their increased incidences of glomerular disease.
 4. National registries have estimated the incidence of pediatric ESRD at 15 cases per 1 million per year.
 5. The 10-year survival rate for adolescent-onset ESRD is 80%.
 6. Cause of ESRD varies by age:
 - a. Infants and young children have increased rates of structural anomalies of the kidneys and urinary tract.
 - b. Older children and adolescents are more likely to have glomerular disease.
- D. Pathophysiology
1. CKD progression is based on the severity of the initial renal damage, the extent of nephron loss, and the age of nephron loss. Combined, these limit the renal reserve. There is also increased risk of progression of existing CKD when superimposed on AKI.
 2. The extent of injury can result from a single episode (acute glomerulonephritis) or from continuous injury (VUR).
 3. Host susceptibility, genetics, duration of disease before prognosis, time to intervention, hypertension, and proteinuria can all influence the progression of disease.
 4. Periods of rapid growth (infancy, puberty) can result in deterioration because of the increased filtration demands on the remaining nephron units.
 5. Presentation of clinical and laboratory features of CKD assists in early diagnosis and can provide clues regarding the underlying etiology.
- E. Diagnosis
1. The classic workup of urine output and laboratory markers, including electrolytes and BUN/SCr, and calculation of GFR are still widely accepted methodologies. Alternative GFR calculators may be found on the National Kidney Foundation (NKF) website (https://www.kidney.org/professionals/KDOQI/gfr_calculator) and include creatinine, cystatin C, and creatinine–cystatin C combination-based formulas as well as the MDRD. Make sure to use the correct equation as not all are validated for children less than 18 years of age. The correct equations by age are clearly delineated on the NKF website.
 2. Limitations to the above assessment strategies in pediatric patients have led researchers to seek out more novel, more accurate, and less invasive ways to diagnose and stage CKD. Renal biomarkers are one area of rapid growth and discovery. Some of the most commonly used studies are discussed below. Despite the obvious benefits to biomarker diagnosis, the role of biomarkers in diagnosis and management is still not fully clear; therefore biomarker use should be approached with caution. Serum and urine biomarkers are discussed in more detail in the Acute Kidney Injury section of this chapter.
- F. Cardiovascular Disease in CKD
1. Cardiovascular events account for most deaths in patients with pediatric-onset CKD. The prevalences of cardiovascular events in ESRD are 24.3% and 36.9% in children 0–4 years and 15–19 years of age, respectively. The most common events include arrhythmias (19.6%), valvular heart disease (11.7%), cardiomyopathy (9.6%), and acute cardiac death (2.8%).
 2. KDIGO guidelines suggest that in children with CKD who are not dialysis-dependent, therapy with blood pressure–lowering drugs should be initiated when the blood pressure is consistently above the 90th percentile for age, sex, and height. For these children, the blood pressure goal is to consistently achieve systolic and diastolic readings at the 50th percentile or less for age, sex, and height.
 3. The Chronic Kidney Disease in Children (CKiD) longitudinal study of children with mild to moderate CKD showed that hypertension is present in 54% of patients in the early stages of CKD.

- a. The ESCAPE trial (Effect of Strict Blood Pressure Control and ACE Inhibition on Progression of Chronic Renal Failure in Pediatric Patients) evaluated ramipril dosed at 6 mg/m²/day in 385 children with CKD ages 3–18 years of age. Patients were randomized to receive conventional or strict blood pressure control. The conventional group targeted blood pressures in the 50th–95th percentile, and the strict control group targeted blood pressures below the 50th percentile according to 24-hour mean arterial pressure for height and sex. Only 29.9% of the patients in the strict blood pressure group versus 41.7% (HR, 0.65; CI, 0.44–0.94; p=0.02) in the conventional treatment group attained the composite end point of doubling of SCr, GFR decline to less than 10 mL/minute/1.73 m², or need for renal replacement therapy. This corresponded to a 5-year rate of delay in the progression of renal disease of 70.1% versus 58.3% (p=0.02). The corresponding risk reduction was 35%.
 - i. The updated KDIGO 2021 Blood Pressure in CKD guidelines cite the ESCAPE trial for their recommendation for goal 24-hour ambulatory mean arterial pressure (measured using ambulatory blood pressure monitoring) in children as equal to or less than the 50th percentile of normal children with corresponding age, sex, and height.
 - ii. The guideline authors state evidence is lacking to support benefit of this goal outside of the CKD patient population represented in the ESCAPE trial.
 - iii. It also recommended that children with CKD have ambulatory blood pressure monitoring yearly, supplemented by standardized auscultatory office blood pressure every 3–6 months. For children too young or unable to tolerate ambulatory blood pressure monitoring then a target systolic blood pressure of less than the 90th percentile for age, sex, and height is the goal.
 - b. Treatment with a single blood pressure–lowering agent controls blood pressure in less than half of patients. Patient with severe hypertension (greater than 20/10 mm Hg above the normal range) should be initiated on combination therapy. In patients with CKD, the RAAS antagonists are most often combined with a diuretic or calcium channel blocker; however, the KDIGO guidelines do recommend first line therapy to begin with an ACEI or ARB before other drug classes are added..
 - c. Combined RAAS blockade with ACEIs and ARBs minimally affects blood pressure but may increase the antiproteinuric effects of ACEI or ARB monotherapy by 30%–40%. In adult trials with diabetic patients, the combination increased the risk of AKI. The ONTARGET study, which compared ACEI monotherapy with ACEI and ARB combination therapy, found no benefit.
 - d. A recent study showed that RAAS blockade reduced the risk of initiation of renal replacement therapy in children by 21% (HR, 0.79) to 37 % (HR, 0.63) from standard regression adjustment and Cox marginal structural models, respectively (Pediatr Nephrol 2017; 32:643–649).
- G. Dyslipidemia in CKD
1. Patients with CKD have an increased burden of atherosclerotic cardiovascular disease. Dyslipidemia is a known risk factor for atherosclerosis and is common among both adult and pediatric patients. Some evidence suggests that dyslipidemia contributes to the initiation and progression of CKD itself.
 2. Accelerated atherosclerosis in children with CKD is likely. Atherosclerosis begins during childhood, and dyslipidemia is a risk factor for its development.
 3. Young adult survivors of childhood ESRD experience a high rate of premature mortality because of atherosclerotic cardiovascular disease, which is their principal cause of death.
 4. The CKiD study evaluated 391 children 1–16 years of age. All children had a diagnosis of CKD. The authors found that overall, 45% of children were dyslipidemic. Thirty-two percent of children had high triglycerides, and 21% had lower HDL. Lower GFR concentrations were associated with increased prevalence of dyslipidemia and increased risk of combined dyslipidemia (several abnormal lipid measures).
 5. The 2012 KDIGO guidelines recommend evaluation of a lipid panel in all children with a new diagnosis of CKD, including children undergoing dialysis or after kidney transplantation, on a yearly basis. The goal lipid concentrations suggested are listed in Table 6.

Table 6. Goal Plasma Lipid Concentrations for Children and Adolescents^a

Parameter	Acceptable	Borderline High (75%)	High (95%)
Total cholesterol	< 170	170–199	≥ 200
LDL	< 110	110–129	≥ 130
Non-HDL	< 120	120–144	≥ 145

^aValues given are in milligrams per deciliter.

- Despite our increasing knowledge about the risk of dyslipidemia in children with CKD, no randomized controlled trials evaluating lipid-lowering therapy to date are available. Therefore the 2012 KDIGO guidelines recommend against the use of statins or statins in combination with ezetimibe in children younger than 10 years. They state that boys older than 10 years and postmenarchal girls with severely increased LDL who have risk factors for cardiovascular events could be candidates. If statin therapy is used, the lowest starting dose is suggested.

H. Anemia in CKD

- Anemia is a common complication of CKD and increases in prevalence with progression of disease.
- Erythropoietin deficiency, blood loss, iron deficiency, bone marrow suppression, malnutrition, inflammation, uncontrolled hyperparathyroidism, malnutrition, inadequate dialysis, and ongoing systemic disease are all contributors to anemia in these patients.
- Chronic anemia can dramatically decrease quality of life. Children with anemia may experience fatigue, impaired cognition, and difficulty with schoolwork. They may also have sleep disturbances, decreased exercise tolerance, depression, and poor appetite.
- The CKiD studies have found a high prevalence of anemia in moderate CKD. Various authors using the CKiD participant database have analyzed the relationship between anemia and CKD. Anemia in CKD increases with decreasing GFR. Hemoglobin declines linearly below a GFR of 43 mL/minute/1.73 m², regardless of age, race, sex, and underlying diagnosis. A 2010 study showed that, on average, a 20% decrease in GFR was associated with a 0.2- to 0.4-g/dL decrease in hemoglobin (Am J Kidney Dis 2010;55:1009-17).
- A 2007 study showed that, compared with white children, African American children tended to have a 0.6 g/dL lower mean hemoglobin concentration despite having been matched for anthropometric, socioeconomic, and clinical status (Am J Hematol 2007;82:611-4).
- Another study of children showed that children with CKD and anemia were 55% more likely to be hospitalized than were children with CKD who did not have anemia (defined as a hematocrit less than 33%).
- Currently, there are no prospective trials to guide the goal hemoglobin value in children with CKD, and instead, KDIGO guidelines use targets extrapolated from adult trial data. For pediatric patients with CKD, the target hemoglobin is 11–12 g/L, though in the KDIGO commentary, the authors state a softer range of 11–13 g/dL, accepting that dose titration to such a narrow window is difficult. The guidelines define anemia in children with CKD as a hemoglobin concentration of less than 11 g/dL in children 0.5–5 years of age, less than 11.5 mg/dL in children 5–12 years of age, less than 12 mg/dL in children 12–15 years of age, and less than 13 g/dL in boys greater than 15 years of age and less than 12 g/dL in girls greater than 15 years of age..
- The current KDIGO recommendations are to consider initiating erythropoiesis-stimulating agent (ESA) therapy when the serum hemoglobin is 9–10 g/dL in all children.
- A retrospective cohort study of children in the United States undergoing hemodialysis between 2000 and 2008 evaluated patient outcomes stratified by hemoglobin level. These authors found a decreased HR for all-cause mortality (0.33, 95% CI 0.14-0.81) and adjusted relative rate of all-cause hospitalizations (0.91, 95% CI 0.74-0.89) in the group with hemoglobin level greater than 12 g/dL. They concluded that for children undergoing hemodialysis, hemoglobin 12 g/dL and above is not associated with increased cardiovascular visits, mortality, or all-cause and cardiovascular-related hospitalizations (Kidney Int 2017;91:177-82).

10. ESAs, including both darbepoetin alfa (Aranesp) and epoetin alfa (Procrit, Epogen), have been studied in pediatric patients with anemia resulting from CKD. Despite very limited studies in pediatric patients, their use is widespread. North American Pediatric Renal Trials and Collaborative Studies data have shown that of 3650 index pediatric dialysis patients, 89.4% were started on ESA therapy by day 30.
 - a. Both epoetin and darbepoetin have proved effective in increasing serum hemoglobin in pediatric patients. In comparator studies, darbepoetin was non-inferior to epoetin in prospective trials in which an increase in serum hemoglobin concentration was the primary outcome measure.
 - b. Despite what seem to be obvious implied subjective benefits to improving hematocrit in anemic children with CKD (increased quality of life, decreased fatigue), these outcomes are rarely used as end points in prospective trials.
 - c. Dosing recommendations from KDIGO are to initiate epoetin alfa at 20–50 international units/kg three times weekly or darbepoetin alfa at a dose of 0.45 mcg/kg once weekly or 0.75 mcg/kg every 2 weeks.
 - i. Doses may be given intravenously or subcutaneously.
 - ii. Dosing should be titrated on a monthly basis.
 - iii. Infants may require higher ESA doses to achieve target goals.
 - iv. Note that many centers are using more aggressive dosing strategies on the basis of experience and physician preference.
11. Iron therapy is required in pediatric patients with CKD. Children with CKD on ESAs are at increased risk of iron deficiency anemia.
 - a. ESAs are known to deplete iron stores, and patients with CKD have decreased oral absorption.
 - b. Iron therapy is recommended by KDIGO when the transferrin saturation is 20% or less and ferritin is 100 ng/mL or less for all pediatric patients with CKD with anemia not on iron or ESA therapy.
 - c. The KDIGO guidelines recommend oral iron (or intravenous iron in HD patients with CKD HD) administration to maintain transferrin saturation greater than 20% and ferritin concentration greater than 100 ng/mL.
12. Recommended dosing of enteral iron replacement is provided in the KDIGO guidelines.
 - a. Iron replacement should be initiated with oral iron at 3–6 mg of elemental iron/kg/day for a trial of 3 months.
 - b. The guidelines suggest once-daily dosing, though iron is often divided into two or three daily doses
 - c. At the end of 3 months, if the transferrin saturation or ferritin concentration has not improved, a switch to intravenous iron therapy is recommended.
13. Intravenous iron product choice or replacement dosing is not provided in the KDIGO guidelines.
 - a. Sodium ferric gluconate therapy was assessed in a 2005 randomized, double-blind, parallel-group trial that evaluated the comparative effectiveness and safety of 1.5 mg/kg versus 3 mg/kg sodium ferric gluconate on hemoglobin concentrations in iron-deficient pediatric patients with ESRD 2–15 years of age who were undergoing HD and receiving concomitant ESA therapy with epoetin alfa (Pediatr Nephrol 2005;20:1320-7). Results show that 1.5 mg/kg and 3 mg/kg were equally effective in increasing baseline hemoglobin at the 4-week evaluation (0.9 g/dL, $p=0.0179$ for 1.5 mg/kg; 1 g/dL, $p=0.0006$ for 3 mg/kg). Because of these similar results, the authors recommend that the lower 1.5 mg/kg be the initial dose used in pediatric patients. No child experienced an allergic reaction, and no child was removed from the study because of an adverse reaction.
 - b. Iron sucrose was studied in children with CKD in a 2013 prospective, randomized, multicenter open label trial (Am J Kidney Dis 2013;61:588-97). The study compared doses of 0.5 mg/kg, 1 mg/kg, and 2 mg/kg of iron sucrose in pediatric patients with CKD undergoing HD. The maximum dose allowed was 100 mg. They found that the 0.5-mg/kg dose given every other week was noninferior to the higher dosing groups in maintaining hemoglobin concentrations greater than 10.5 mg/dL.
 - c. Newer iron-based phosphate binders such as ferric citrate and sucroferric oxyhydroxide may provide another mechanism of iron delivery in the future.

I. Growth and Nutrition in CKD

1. Cachexia and protein-energy wasting are described in adult patients; however, data concerning the prevalence in children with CKD is limited. Anorexia in infants may be related to altered taste, oral food aversions, gastroesophageal reflux, delayed gastric emptying, and altered appetite-regulating hormones. Aggressive nutrition management with the guidance of qualified pediatric dietitians is critical.
2. The Kidney Disease Outcomes Quality Initiative (KDOQI) pediatric nutrition clinical practice guidelines are available to assist the practitioner caring for infants, children, and adolescents with stage 2–5 CKD, on long-term dialysis therapy, or with a kidney transplant (<https://www.kidney.org/sites/default/files/docs/cpgpednutr2008.pdf>).
3. Decreased linear growth is another concern in children with CKD. The mean height of children with CKD is 1.5 SDs below the mean. Contributing factors include age of onset of CKD, duration of CKD, metabolic acidosis, drug exposures (including glucocorticoids), associated genetic disorders, protein-calorie malnutrition, and hormonal disturbances. Short stature is the most common concern regarding quality of life among survivors of pediatric-onset CKD.
4. The KDOQI guidelines recommend the following regarding the use of recombinant human growth hormone (GH) in children with CKD.
 - a. Should be considered in children with stage 2–5 and 5D CKD with short stature and potential for linear growth if growth failure persists beyond 3 months, despite treatment of nutritional deficiencies and metabolic abnormalities
 - b. Children should have hip radiographs and a wrist bone age performed before GH therapy is initiated.
 - c. GH initiation requires parathyroid hormone (PTH) and phosphorus to be controlled with a PTH concentration less than 2 times the target upper limit for stage 2–4 CKD or 1.5 times (450 pg/mL) the target upper limit in stage 5 CKD and phosphorus less than 1.5 times the upper limit for age.
 - d. Recommended monitoring for GH therapy in children with stage 2–4 CKD includes calcium, phosphorus, PTH, and alkaline phosphatase every 3 months during the first year of therapy. For children with stage 5 CKD, the recommendation is as above, but monitoring should be done monthly.
 - e. Children undergoing GH therapy should have a wrist bone age performed yearly. Hip radiographs should be done when clinically indicated.
 - f. GH therapy should be discontinued temporarily:
 - i. Stage 2–4 CKD: If the patient's PTH concentration is greater than 400 pg/mL, GH should not be reinitiated until the PTH concentration is 200 pg/mL or less.
 - ii. Stage 5 CKD: If the patient's PTH concentration is greater than 900 pg/mL, GH should not be reinitiated until the PTH concentration is 50 pg/mL or less.
 - iii. In all stages of CKD, if a slipped capital femoral epiphysis or symptomatic high-turnover renal osteodystrophy occurs
 - g. GH therapy should be discontinued permanently when the epiphyses are closed.

J. Bone Health in CKD

1. Pediatric patients with CKD are at risk of metabolic bone disease (CKD-MBD). Chronic hyperphosphatemia begins in stage 3 kidney disease and will lead to increased PTH and fibroblast growth factor-23 (FGF-23) as well as decreased $1,25(\text{OH})_2\text{D}$. In pediatric CKD, the conversion of $25(\text{OH})\text{D}$ to $1,25(\text{OH})_2\text{D}$ is impaired and reduces the absorption of calcium in the intestines, which also further increases PTH and FGF-23. The kidney cannot respond adequately to PTH to promote phosphaturia and calcium reabsorption. The kidney also does not respond to FGF-23. FGF-23 is responsible for promoting calcium retention and phosphorous excretion. This leads to long-term dysregulation of bone formation during growth in children or alterations in bone structure and function during adulthood. All children with stage 5 CKD HD and most patients with stage 3–5 CKD will have CKD-MBD. The ultimate consequence of uncontrolled CKD-MBD may be extraskeletal calcification that results from

- the deranged mineral and bone metabolism and from the therapies used to correct it. The combination of mineral metabolism disorder, fractures, and cardiovascular disease may contribute to increased morbidity and mortality in patients with CKD.
2. Laboratory values will show increased phosphorus, normal to low serum calcium, and a high serum PTH. The serum PTH increases with decreasing GFR. Radiography will reveal osteomalacia/osteopenia of the bones with corresponding soft tissue calcification.
 - a. Routine monitoring of serum calcium, phosphorus, PTH, and alkaline phosphatase activity should begin in stage 2 CKD.
 - b. The frequency of monitoring should increase as CKD stage increases and according to the presence and magnitude of abnormalities. For example, in dialysis-dependent children with stage 5 CKD, it is recommended that serum calcium and phosphorus be checked every 1–3 months and PTH every 3–6 months.
 - c. Children's growth should be followed to assess for linear growth suppression.
 - d. Goals of therapy
 - i. For patients with stage 3–5 CKD, serum calcium and phosphorus concentrations should be kept in the normal range. The optimal PTH concentration is unknown, but it is recommended that with an intact parathyroid hormone (iPTH) concentration above the upper limit of normal be evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency.
 - ii. For children who are dialysis-dependent, the KDIGO guidelines recommend a softer goal of lowering phosphorus toward the normal range but state that calcium should be kept in the normal range. The iPTH goal for these children is given as 2–9 times the upper normal limit for the assay.
 - (a) Normal PTH range is not well defined in the literature. Commentary from Rees in 2008 suggests that a normal range of 10–65 pg/mL was most commonly used in studies published since 1990.
 - (b) These studies included very few young children, and the studied patients were heterogeneous with respect to disease states, age, and management.
 - (c) Calcium management strategies have changed since 1990, which may make extrapolation difficult.
 - (d) Over the years, the assays for PTH measurement have undergone changes, which increases the difficulty of interpretation in children, already an understudied population.
 3. Treatment of CKD-MBD includes restriction of dietary phosphorus, use of phosphate-binding agents, and use of vitamin D precursors such as ergocalciferol, calcimimetics (activators of calcium receptors on parathyroid cells), and bisphosphonates.
 - a. Phosphate binders: Taken with meals to bind phosphorus in the gut. May combine different products for additive effects
 - i. Calcium-containing phosphate binders
 - (a) Calcium carbonate (Tums)
 - (1) Inexpensive
 - (2) Flavor and ability to chew tablets may be accepted by children more readily. Suspension is available as a 1250-mg/5 mL salt made by various manufacturers that can have different flavors.
 - (3) Each 500 mg of calcium carbonate equals 200 mg of elemental calcium. Monitor for potential errors with salt and elemental dosing of agents.

- (b) Calcium acetate
 - (1) Increased efficacy compared with calcium carbonate
 - (2) Available as 667-mg calcium acetate capsules (PhosLo), which contain 169 mg of elemental calcium per capsule, or as a calcium acetate solution (Phoslyra), which contains 667 mg (169 mg elemental)/5 mL. The solution is black cherry flavor. Phoslyra is not labeled for pediatric use. Cost is prohibitive for some patients.
- ii. Non-calcium-based non-absorbable phosphate binders. Considered if hypercalcemia or calcium phosphorus product is greater than $55 \text{ mg}^2/\text{dL}^2$. Use of the calcium phosphorus product is not recommended in the KDIGO guidelines but is recommended in the KDOQI guidelines as an opinion-level recommendation.
 - (a) Calcium phosphorus product is calculated by multiplying the corrected serum calcium (milligrams per deciliter) by the serum phosphorus (milligrams per deciliter).
 - (b) The final product is suggested to be less than $55 \text{ mg}^2/\text{dL}^2$ in patients with CKD older than 12 years and less than $65 \text{ mg}^2/\text{dL}^2$ in younger children.
 - (c) A high calcium phosphorus product can result in soft tissue calcification.
 - (d) Sevelamer (Renagel, Renvela)
 - (1) Available as a large 400- or 800-mg tablet of sevelamer HCl (Renagel), as an 800-mg tablet sevelamer carbonate (Renvela), or as a 0.8- or 2.4-g/packet powder for suspension sevelamer carbonate (Renvela)
 - (2) Renvela, which has a “citrus cream flavor” that most children find unappealing, requires 30–60 mL of water to dilute each packet, which can be difficult for small children.
 - (3) The tablets may not be crushed, and they can expand in the throat if not swallowed well, so they should be avoided in children who are not confident in their pill-swallowing technique.
 - (e) Lanthanum carbonate (Fosrenol)
 - (1) No pediatric dosing information available; not FDA approved
 - (2) Available as 500-, 750-, or 1000-mg chewable tablets. The tablets are not flavored and must be chewed down to liquid consistency before being swallowed. The taste is quite chalky and unappealing.
 - (3) Animal studies have shown lanthanum deposition into developing bone, including growth plate. The FDA posted concerns with long-term deposition in the GI tract in adults as well. For this reason, it is not recommended for use in children. Abdominal radiographs of patients taking lanthanum may have a radiopaque appearance typical of an imaging agent. Patients with acute peptic ulcers, ulcerative colitis, Crohn disease, and bowel obstruction were not included in lanthanum clinical studies.
- iii. Newer phosphate binders are under development and review, including iron-based binders (sucroferric oxyhydroxide, ferric citrate, and iron magnesium hydroxycarbonate) and an anion-exchange resin (colestilan [MCI-196]).
- b. Vitamin D, vitamin D analogs, and calcimimetics
 - i. Ergocalciferol (vitamin D_2 , Drisdol) – May be less potent and have a shorter duration of action than cholecalciferol. The liquid contains 200 IU (5 mcg)/drop or 8000 IU/mL. The dropper provided with the bottle delivers 40 drops/mL. Caution for mix-up dosing errors. A single bottle typically lasts 20 days and costs about \$150. There are also ergocalciferol capsules (50,000 IU and 1.25 mg), which are more affordable.
 - ii. Cholecalciferol (vitamin D_3 , Just D, D-Vi-Sol) – Available in various strengths, but the most common liquid products, Just D and D-Vi-Sol, are 400 IU/mL. Although cholecalciferol preparations are less expensive than ergocalciferol, some patients will require several tablets/capsules or a larger liquid volume to achieve the desired dose.

- iii. Calcitriol (1,25-dihydroxycholecalciferol, Rocaltrol, Calcijex) – Activated form of vitamin D₃ that does not require liver or kidney activation. Available as a 1-mcg/mL oral solution or as 0.25- and 0.5-mcg capsules. The solution is unflavored, but fortunately, for children, the dose volume is minimal. The bottle size of 15 mL can typically last at least 1 month, but prices vary from \$100–\$200 per bottle. Calcitriol (Calcijex) is also available as a 1-mcg/mL (1 mL) ampule for intravenous injection, which can be used for dialysis-dependent children.
- iv. Paricalcitol (Zemlar) – Selective vitamin D receptor activator that increases calcium phosphorous product with less-sustained hypercalcemia than vitamin D supplements
 - (a) Indicated for adults with stage 3 or higher CKD. No indication in children
 - (b) Limited but positive safety studies in children. A recent multinational trial showed good efficacy and tolerability in children 10–16 years of age with stage 3–5 CKD and reduced iPTH levels. The authors recommend an initiation dose of 1 mcg by mouth three times weekly in children 10–16 years old (Pediatr Nephrol 2017;32:1221-1232).
 - (c) Available as 1-, 2-, and 4-mcg capsules and 2-mcg/mL and as a 5-mcg/mL injectible.
- v. Cinacalcet (Sensipar) – Calcimimetic agent that binds with the calcium-sensing receptor on the parathyroid gland and increases the receptor sensitivity to serum calcium concentrations, which reduces PTH, calcium, and phosphorus
 - (a) May be useful in children with high calcium and phosphorus concentrations, as well as high PTH concentrations
 - (b) Indicated for adults with stage 5 CKD (dialysis-dependent).
 - (c) The FDA placed a clinical hold, beginning in February 2013, on all pediatric clinical studies of Sensipar (cinacalcet hydrochloride) because of the death of a pediatric patient involved in a study. Causality has not been assigned. The manufacturer is currently seeking FDA approval for pediatric patients.
 - (d) Close monitoring of calcium, phosphorus, and PTH levels are recommended if therapy is initiated.
 - (e) Available as 30-mg tablets. May also be prepared as an extemporaneous compound
- vi. Bisphosphonates – Non-hydrolyzable pyrophosphate analogs that can prevent both the formation and precipitation of calcium phosphate and the dissolution of calcium phosphate crystals. Bisphosphonates also bind to bone and inhibit osteoclast-mediated calcium reabsorption.
 - (a) The role of bisphosphonates is unclear because the mechanism of osteoporosis in pediatric patients differs from that in adult patients (primarily as a long-term adverse effect of glucocorticoids).
 - (b) Both pamidronate and ibandronate have been reported with successful use for the treatment of acute hypercalcemia and calciphylaxis (calcific uremic arteriopathy, which manifests as painful non-healing eschars in association with panniculitis and dermal necrosis) in pediatric patients with CKD.
 - (c) There is no consensus regarding the optimal bisphosphonate agent, dosage, or therapy duration in children
 - (d) CKD is a contraindication to bisphosphonate use because bisphosphonates are renally cleared, and skeletal accumulation, effects on longitudinal growth, and worsening renal impairment are the most troublesome risks of therapy. They should be used with extreme caution.

Patient Case

9. M.M. is a 16-year-old male HD-dependent patient (weight 82 kg) who has had ESRD for 2 years and is awaiting a kidney transplant. He has a history of hypertension, hyperlipidemia, and anemia. Lately the nephrologists have been struggling to get M.M.'s serum phosphorus concentration under control, and adherence is an issue. Medications are as follows: epoetin 20,000 units three times weekly at dialysis, calcitriol 3 mcg intravenously three times weekly at dialysis, B-complex with C multivitamin once daily, pravastatin 20 mg/day, ramipril 5 mg/day, amlodipine 10 mg/day, and calcium acetate 1334 mg three times daily with meals. Laboratory values are as follows: hemoglobin 9.8 g/L, iPTH 1100 pg/mL, sodium 142 mEq/L, potassium 4.3 mEq/L, SCr 4.1 mg/dL, calcium 10.8 mg/dL, albumin 2.5 g/L, and phosphorus 6.9 mg/dL. In addition to enforcement of adherence to both medications and diet, which is the best approach to managing this patient's hyperparathyroidism and renal osteodystrophy?
- A. Increase calcium acetate.
 - B. Add ergocalciferol 50,000-unit capsule by mouth once weekly.
 - C. Change calcium acetate to sevelamer carbonate and add cinacalcet.
 - D. Change calcium acetate to sevelamer.

VII. RENAL REPLACEMENT THERAPY

- A. Indications for Renal Replacement Therapy
 - 1. A – acidosis that is not responsive to bicarbonate
 - 2. E – electrolyte abnormalities (typically hyperkalemia or hyperphosphatemia)
 - 3. I – intoxication with dialyzable toxin or inborn errors of metabolism
 - 4. O – fluid overload (symptomatic)
 - 5. U – uremia
- B. Modes of Dialysis in Children
 - 1. HD
 - 2. PD
 - 3. CRRT
- C. Hemodialysis
 - 1. Access
 - a. Arteriovenous fistula
 - i. Formed by anastomosis of artery and vein. Typically placed in the forearm or upper arm
 - ii. Lowest incidence of thrombosis and infection, as well as longest survival and lowest cost
 - iii. Make take weeks to months to mature. Lack of maturation is the No. 1 reason for underuse in children, and lack of access to an experienced pediatric vascular surgeon is a barrier to use.
 - iv. Visible on the forearm
 - b. Arteriovenous graft
 - i. A looped plastic (commonly expanded polytetrafluoroethylene) tube that connects an artery to a vein
 - ii. Used when patients have small or weak veins that will not properly develop into a suitable fistula
 - iii. Typically can be used 2–3 weeks after surgery
 - iv. Increased risk of infection and clotting compared with an arteriovenous fistula

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- c. Central venous catheters
 - i. Non-tunneled lines are typically placed for emergency dialysis when permanent access is not available.
 - ii. They have high rates of infection and thrombosis.
 - iii. Thrombosis can lead to incomplete dialysis.
 - 2. Hemodialysis prescription and considerations in children
 - a. Hemodialysis involves principles of both diffusion (small solute removal) and convection/ultrafiltration (fluid and middle molecular weight removal). In hemodialysis, a dialyzer machine and an extracorporeal circuit are used to allow blood and a dialysate solution to be exposed to each other on the opposite sides of a semipermeable membrane in a countercurrent direction. This maximizes the concentration gradient and permits toxin/solute removal. Fluid is removed through ultrafiltration, which occurs by means of transmembrane pressure created by the dialyzer machine.
 - b. Goal is measured in terms of urea clearance. Adequacy is generally assessed monthly in pediatric CKD patients but may be assessed daily if necessary during acute HD.
 - c. Usual blood flow rates (Q_B) are 6-8 mL/kg/min and dialysate flow rates are typically 1.5-2× the blood flow rate.
 - i. The extracorporeal blood flow rate, the duration of the session, and the number of sessions per week is progressively increased over time, as the patient tolerates, to meet patient specific needs or goals.
 - ii. Standard or intensified urea removal may be used, depending on specific patient needs regarding solute clearance, fluid removal, and growth/nutrition. Intensified HD has been associated with improved growth and nutrition in children.
 - iii. Disequilibrium syndrome can occur, and symptoms vary widely, from restlessness and headache to coma and death.
 - d. Lines and tubing are available in sizes for every pediatric patient from infants to large adolescents. Prescribers choose tubing on the basis of patient size/tubing contribution to extracorporeal circuit volume, biocompatibility, and type of sterilization. The goal total extracorporeal blood volume (needles, tubing, and dialyzer) should be less than 10% of the patient's total blood volume.
 - e. Anticoagulation of the extracorporeal circuit is most commonly achieved with unfractionated heparin.
 - f. Commercially available dialysate solutions are preferred over pharmacy-customized or compounded solutions to minimize the risk of error and maximize sterility. The nephrologist can choose from a range of products that vary by buffer type and calcium and dextrose content.
 - 3. Factors affecting the efficiency of HD
 - a. Blood flow rate
 - b. Dialysis flow rate
 - c. Filtration flow rate
 - d. Type of dialyzer membrane and material
 - e. Duration of session
 - 4. Acute complications of HD
 - a. Hypotension
 - b. Nausea/vomiting
 - c. Cramping
 - d. Infection, typically with central venous catheter lines
-

D. Continuous Renal Replacement Therapy

1. CRRT is often the preferred RRT modality in the acute care setting because of its lesser impact on hemodynamics and continuous nature, which permits more targeted management of overall fluid and nutrition status.
2. Types of CRRT
 - a. Slow continuous ultrafiltration (SCUF) removes fluid without the need for replacement fluids. This can help prevent or treat fluid overload when waste products do not need to be removed or when the pH concentration does not need to be corrected.
 - i. Ultrafiltration is the movement of water across a semipermeable membrane by means of osmotic pressure.
 - ii. The pressure gradient is known as the transmembrane pressure gradient.
 - iii. The fluid removed is called the ultrafiltrate.
 - b. Continuous venovenous hemofiltration (CVVH) – Removes fluids and waste from the patient through convection. It then uses replacement fluids to maintain electrolyte, fluid, and acid-base balance.
 - i. In convective clearance, water is moved across a semipermeable membrane by means of transmembrane pressure gradient and solute is “dragged” (solvent drag) with the water.
 - ii. Both small-molecular-weight substances (urea, creatinine, potassium) and medium- to large-molecular-weight substances (inulin, tumor necrosis factor, microglobulin) can be removed.
 - iii. Some use the term *hemofiltration* to describe convective clearance with a high ultrafiltration rate.
 - iv. Higher ultrafiltration rates increase convective clearance, and the replacement fluids, which contain electrolytes and buffer (lactate or bicarbonate), create a new blood chemistry profile for the patient.
 - c. Continuous venovenous hemodialysis (CVVHD) primarily uses diffusion between blood and a dialysate solution to facilitate the removal of waste products through concentration gradients.
 - i. Diffusive clearance features solute moving across a semipermeable membrane by means of a concentration gradient (from higher concentration to lower). Conventional dialysis membranes which utilize diffusive clearance are most efficient at removal of low molecular weights (below 500 daltons).
 - ii. The dialysate runs countercurrent to the blood flow.
 - iii. Dialysate solutions typically reflect normal plasma values.
 - d. In continuous venovenous hemodiafiltration (CVVHDF), fluid and waste are removed from the patient by means of a combination of convection and diffusion. This allows the removal of large volumes of plasma while maintaining electrolyte balance.
3. CRRT impact on pharmacokinetic parameters
 - a. Circuit prime and volume of distribution
 - i. Usual circuit priming volume: About 100–150 mL
 - (a) Blood or saline prime is chosen, depending on the child’s age or size.
 - (b) Circuit volume may be greater than 10%–15% of patient blood volume.
 - ii. Usual adult blood volume: Around 5000 mL (0.07 L/kg or 70 mL/kg)
 - iii. Usual pediatric blood volume: Around 80 mL/kg
 - b. Impact of tubing and membrane filter
 - i. Tubing may bind drug and increases volume of distribution.
 - ii. Adsorption
 - iii. Membrane filter binds drug by means of the Gibbs-Donnan effect.
 - (a) Depends on charge of drug
 - (b) Saturation may occur after 30–60 minutes.

- c. Impact of blood flow and circuit flow rates
 - i. Usual blood flow rate is 3–5 mL/kg/minute. Rates tend to be higher in infants (10–12 mL/kg/minute) than in older children (4–6 mL/kg/minute). An increase in blood flow rate leads to increased clearance. The minimum blood flow rate is 30–50 mL/minute to minimize circuit clotting.
 - ii. The ultrafiltrate rate approximates the filter replacement fluid rate, which is 35–45 mL/kg/hr (1500–3000 mL/1.73m²/hour). Higher rates lead to increased clearance.
 - iii. Dialysate rates are 20–30 mL/kg/hour (1500–3000 mL/1.73m²/hour). Higher rates lead to increased clearance.
 - iv. Note that, on average, combined rates of ultrafiltration and dialysate typically do not exceed 35 mL/kg/hour (2000 mL/1.73m²/hour). Goals are institution- and patient-specific and are extrapolated from adult data.
4. Estimating drug clearance on CRRT
 - a. Convective clearance (filter replacement fluid)
 - i. Small- to middle-weight molecules and low-protein-bound drugs pass freely through the membrane filter.
 - ii. Clearance depends on protein binding, independent of molecular weight.
 - (a) Drug concentration in filtrate = C_f
 - (b) Drug concentration in plasma entering the dialysis filter = C_p
 - (c) $S = C_f/C_p$
 - (d) $Cl_f \text{ mL/min} = Q_f \text{ mL/min} \times S$
 - (1) Q_f is the ultrafiltrate rate in milliliters per minute and equals the filter replacement fluid rate in milliliters per minute
 - (2) Q_f depends on membrane surface area and transmembrane pressure.
 - b. Diffusive clearance (dialysate)
 - i. Clearance (Cl_d) depends on the dialysate saturation (S_d). Small molecules, including small, low-protein-bound drugs, pass through the membrane filter by means of diffusion and pressure.
 - ii. Clearance depends on protein binding, volume of distribution, and molecular weight. Drugs that are highly protein bound (greater than 80%) and/or have a large Vd (greater than 1 L/kg) are unlikely to be removed to a significant degree. Very large molecules (greater than 15,000 Da) are less likely to be removed than smaller ones (less than 500 Da).
 - (a) Drug concentration in dialysate = C_d
 - (b) Drug concentration in plasma = C_p
 - (c) $S_d = C_d/C_p$
 - (d) $Cl_d \text{ mL/minute} = Q_d \text{ mL/minute} \times S_d$
 - (1) Q_d is the dialysate rate in milliliters per minute.
 - (2) Q_d depends on membrane surface area, pore size, and blood flow rate.
 - c. Combined hemofiltration plus dialysis (Cl_{df})
 - i. Convective clearance (filter replacement fluid)
 - ii. Diffusive clearance (dialysate)
 - iii. $Cl_{df} = Q_f \times S + Q_d \times S_d$
 - d. Native clearance must be considered if the patient maintains renal function in addition to CRRT support.
 - e. Sieving coefficient
 - i. $S = C_f/C_p$
 - ii. Sieving coefficient defines the clearance of a molecule. A sieving coefficient of 1 means that a molecule passes freely through a semipermeable membrane. A molecule with a sieving coefficient of 0 would not cross.

5. Practical drug dosing for patients on CRRT
 - a. Patients may have some residual renal function, which will contribute to drug excretion. This must be accounted for in dose adjustment. Drugs eliminated predominantly by the renal route will be removed by both kidneys and CRRT, with the greater role being played by the kidneys. As kidney function improves, the percentage of drug eliminated by CRRT declines.
 - b. Previous equations are often used in CRRT pharmacokinetic drug studies but are rarely used at the bedside.
 - c. If specific recommendations for dosing in CRRT are available in tertiary references, they should be used as long as your patient's blood flow rate, filter replacement fluid rate, and dialysate rates approximate what was used in the studies.
 - d. When CRRT dosing is not specifically addressed, references often recommend dosing according to the expected GFR of 10–50 mL/minute/1.73 m². This dosing recommendation, when applied to children, may result in underdosing of medications and should be interpreted with caution.
 - e. Therapeutic drug monitoring can help direct therapy.
 - f. Primary literature may hold some guidance if there is time to review it, and knowing the drug molecular weight, drug protein binding, and filter size can help the clinician formulate an educated plan (Pediatr Drugs 2004;6:45-65).
 - g. Weigh the risks and benefits with the nephrologist and ICU teams when deciding on the dosing range.
 6. Anticoagulation for CRRT
 - a. Usually required to prevent clotting of the extracorporeal circuit
 - b. The goal for anticoagulation in CRRT is to reduce clotting in the hemofilter to avoid interruptions in therapy. Interruptions because of clotting can dramatically reduce the total therapy time (average reduction from 24 hours/day to 16 hours/day) and efficacy of CRRT.
 - c. Decisions regarding whether to use heparin- or citrate-based regimens can depend on the nephrologist's preferences, the center's preference, or specific patient risk factors. Direct thrombin inhibitors can be used in the setting of heparin-induced thrombocytopenia.
 - d. Remember that heparin-based anticoagulation may result in systemic anticoagulation of the patient, whereas citrate-based anticoagulation, which is considered "regional," provides anticoagulation only to the CRRT mechanical circuit itself.
- E. Peritoneal Dialysis
1. PD is the most commonly used dialysis modality for CKD in children younger than 2 years (96%), but the preference is equal to HD as children reach adolescence. When PD is preferred, it is usually for the ability it confers to do home dialysis and the more minimal requirement for clinic time for the child. In infants, a fistula for HD is not feasible because of their small vasculature and because central venous catheters for chronic HD have a high rate of infection and mechanical complication in that age group.
 2. PD has also been shown to have improved growth rates and may better prepare a child to receive a kidney transplant than HD will.
 3. Potential mortality benefit for children undergoing continuous PD compared with that for children undergoing daily intermittent hemodialysis (Pediatr Nephrol 2016;10:1681-9)
 4. PD requires a patent abdominal cavity and a functioning peritoneal membrane across which solute and fluid transport occur. Unique contraindications in pediatric populations include omphalocele, gastroschisis, diaphragmatic hernia, bladder exstrophy, and obliterated peritoneal cavity or membrane failure. Patients with pulmonary compromise should be monitored for clinical worsening because of increased abdominal dialysate volumes, which can prevent full diaphragmatic excursion.

5. PD catheters should be placed by an experienced pediatric surgeon. Placement technique is paramount, because PD catheter infection rates are high in infants and young children. The exit site of the PD catheter must be placed away from the diaper area and any potential gastrostomy site, with the superficial cuff located about 2 cm from the skin surface. Performance of an omentectomy (removal of the omentum, an apron-like fold of visceral peritoneum that hangs down from the stomach) is an area of controversy. The structure may have a natural role in infection prevention but may also lead to catheter complications and infection if it becomes wrapped around the catheter. Right now, omentectomy is routinely performed by about 50% of centers in the United States.
6. The PD prescription
 - a. Type of PD
 - i. Continuous ambulatory PD is the classic form. It requires several manual changes throughout the day. Because of the interruption in school time, this is not commonly used in children.
 - ii. In automated PD, a cycler/machine is used to perform the exchanges. Several types of automated PD are described below. Automated PD is often done in children while they sleep. It can enable small, frequent changes that aid in ultrafiltration. However, the cost of this form of PD can be a barrier to its use.
 - (a) Continuous cycling PD – Exchanges (4–7) are done by the machine overnight, and the PD solution is left in the cavity all day.
 - (1) The child is free from the machine during the day for school.
 - (2) Nighttime exchanges with the patient in the supine position permit larger fill volumes, which increase the recruitment of functional peritoneal surface area.
 - (3) May be associated with less risk of infection than continuous ambulatory PD
 - (b) Nocturnal intermittent PD – Omits daytime dwell owing to good residual renal function or mechanical contraindications
 - (1) May be an option for children who cannot tolerate the higher intra-abdominal pressures associated with the daytime dwell in continuous-cycling PD
 - (2) Reduces glucose absorption and decreases amino acid and protein loss, which may be advantageous in children with hyperglycemia
 - (3) May limit solute clearance, so not optimal in children with lower peritoneal transport
 - (c) Tidal PD – An initial infusion of PD solution into the peritoneal cavity is followed by only partial dialysate drainage, thus always leaving an intra-abdominal reserve volume. Tidal drain volume is replaced with fresh dialysis fluid to restore the initial intraperitoneal volume with each cycle, where the entire dialysate volume is drained at the end of the PD session. The expected amount of ultrafiltrate during each cycle must be estimated and added to the drain volume to prevent overfilling of the peritoneal cavity.
 - (1) Enhanced clearance is possible with this method because of the continuous contact between the peritoneal membrane and the dialysate.
 - (2) This method can reduce pain during the drain phase.
 - (3) Tidal PD can also be used in patients with mechanical outflow problems caused by adhesions or improper catheter placement and in patients with ascites.
 - b. Fill volume
 - i. Adult patients will typically use standard fill volumes for PD, but in infants and children, the exchange volume for PD is scaled by body surface area. If too small a volume of PD is used, rapid equilibration will result, leading to inadequate ultrafiltration. If a volume too large is used, the intraperitoneal pressure can rise, which will also decrease dialysis efficiency because of enhanced lymphatic uptake.
 - ii. The recommended exchange volume for automated PD patients younger than 2 years is 600–800 mL/m². Exchange volume in older children and adolescents is generally exchanged 1000–1200 mL/m².

- c. Dwell time
 - i. Empiric dwell time for automated PD is often set at 1 hour.
 - ii. Removal of higher-molecular-weight solutes requires a longer dwell time.
 - iii. Increasing the frequency of dwells is less effective than increasing the volumes for improvement in CrCl. It is also more expensive and may interfere with the patient's lifestyle.
 - iv. The final determination of dwell time is based on the peritoneal equilibration test, as well as the clinical and laboratory analysis of dialysis adequacy.
- d. PD solution
 - i. Traditional lactate-based buffer solutions have either dextrose or icodextrin as the osmotic agent. Icodextrin is specially used for long dwell time dialysis because its absorption from the peritoneal cavity is much slower than that of dextrose. Icodextrin is rarely used in children because their smaller surface area generally precludes once-daily dwells and prolonged exchange with icodextrin may cause a negative amino acid balance in children. Icodextrin may be considered a supplement to dextrose solution in patients with insufficient ultrafiltration.
 - ii. Commercially available PD solutions have various dextrose amounts, ranging from 1.5%–4.25%, with corresponding osmolalities of 346–483 mOsm/L.
 - (a) Increasing the dextrose percentage of the PD fluid increases the volume of fluid removal per day but may lead to hyperglycemia.
 - (b) Dextrose percentage should be titrated according to the ultrafiltration requirement, patient fluid status, patient nutrition status, and serum blood glucose.
 - iii. The solutions can have “standard” calcium, which is 3.5 mEq/L, or “low” calcium, which is 2.5 mEq/L, depending on patient needs as well.
 - iv. Bicarbonate-based solutions, which are widely available in Europe, are an area of study in pediatric patients. It is hoped that they may provide better buffering with lowered intraperitoneal pressures and therefore may accommodate larger fill volumes.
- e. Drug dosing for patients undergoing PD
 - i. The most recent ISPD guidelines for pediatric patients are from 2012. They cover most antibiotics that may be needed for the treatment of PD catheter infections. Readers should note that these guidelines are now over 10 years old and institutional practices may differ significantly because of this.
 - ii. Clearance for all types of PD is significantly lower than that with HD, so dosing cannot be extrapolated. Patients undergoing automated PD will have increased clearance compared with those undergoing continuous ambulatory PD.
 - iii. If drugs that are highly protein bound are given intravenously instead of intraperitoneally, the drug concentration in the peritoneal dialysate will be low; only the unbound drug can be transported to the peritoneal dialysate. For this reason, when drugs (especially antibiotics) that bind strongly to a protein are administered to continuous ambulatory PD patients with peritonitis, an intraperitoneal route is preferable to an intravenous route.
 - iv. Tertiary references such as *Lexi-Comp's Pediatric and Neonatal Dosage Handbook* and the Renal Pharmacy Consultants' 2022 *Dialysis of Drugs*, may provide referenced recommendations.
- 7. PD associated peritonitis and catheter infections
 - a. Infectious complications are the most common cause of morbidity in pediatric patients undergoing long-term PD. The infection rate in children undergoing PD exceeds the rate in their adult counterparts and is the most common reason for dialysis modality changes in children.
 - b. The 2012 ISPD Consensus Guidelines for the Prevention and Treatment of Catheter-Related Infections and Peritonitis in Pediatric Patients are the primary reference for infection in PD patients.

- c. Among the pharmacy-specific highlights from the extensive guidelines regarding prophylaxis for infection:
 - i. Perioperative prophylactic antibiotics should be administered 60 minutes before incision for PD catheter placement to reduce early-onset peritonitis. The recommended therapy of a first-generation cephalosporin or vancomycin is based on center-specific susceptibility patterns and public health concerns.
 - ii. Maintenance of a long-term PD catheter site care should include routine use of topical antibiotic in accordance with center-specific infection rates. The guidelines specifically mention mupirocin, gentamicin, MediHoney, and Polysporin triple antibiotic. They caution that if the patient has a polyurethane-based catheter, antibiotics containing polyethylene glycol should not be used, because they can cause catheter rupture.
 - iii. Prophylactic antibiotics are also suggested before invasive dental procedures; before GI and genitourinary procedures associated with a high risk of bacteremia; and after accidental intraluminal contamination.
 - iv. If a gastrostomy tube is placed in a child with an existing PD catheter, prophylactic antibiotic and antifungal coverage is recommended. Typically this is a single dose of intravenous cefazolin, with completion of the infusion 60 minutes before incision. If the risk of MRSA is high, vancomycin should be used. Fluconazole prophylaxis is also recommended.
- d. Diagnosis of PD-related peritonitis
 - i. Infection should be suspected if peritoneal effluent is cloudy. Effluent should be sent for culture and cell count to confirm diagnosis. If the effluent white blood cell (WBC) count is greater than 10×10^3 cells/mm³ and at least 50% of the WBCs are polymorphonuclear leukocytes, an empiric diagnosis of peritonitis should be made.
 - ii. Children with peritonitis may report or express abdominal pain that is generalized. Affected children often exhibit guarding and rebound tenderness. There may be constipation, fever, and vomiting.
- e. Recommendations on empiric antibiotic therapy and administration
 - i. The guidelines prefer intraperitoneal installation of antibiotics for the treatment of PD infections because of their more direct delivery to the site of infection. This also allows home-based delivery for children. (See Table 7 for the dosing recommendations.) The pharmacokinetics of β -lactam drugs dosed intermittently in children with automated PD and frequent short cycles is not well described, and there is concern about undertreatment.
 - ii. A dwell time of 3–6 hours is recommended for the loading dose.
 - iii. Empiric therapy should be guided by center-specific antibiotic susceptibility.
 - (a) The first-line therapy recommendation is intraperitoneal cefepime.
 - (b) The second-line choice is a first-generation cephalosporin combined with ceftazidime or an aminoglycoside.
 - (c) An intraperitoneal glycopeptide should be added to cefepime or replace the first-generation cephalosporin if the resistance rate of *Staphylococcus aureus* isolates to methicillin or oxacillin exceeds 10% or if the patient has a history of MRSA infection.
 - iv. Culture-specific therapy – See Figures 2 and 3.
 - v. The duration of therapy, which varies with the organism, is 2–3 weeks.
 - vi. If initial cultures are negative at 72 hours and if signs and symptoms of peritonitis are improved, an empiric 2-week regimen of cefepime, ceftazidime, cefazolin, or a glycopeptide is suggested. Administration of an aminoglycoside may be discontinued at 72 hours if the patient's culture is negative and clinical improvement is noted.

- vii. Fungal peritonitis requires early catheter removal and treatment with antifungal therapy for 2 weeks or longer after complete resolution of clinical symptoms. The guidelines are not directive of which antifungal to use but mention that intraperitoneal amphotericin B can be irritating to the peritoneum and cause severe abdominal pain. Treatment with fluconazole or an echinocandin is a more appropriate first-line therapy, with a change to posaconazole or voriconazole if *Aspergillus* or a nonresponding strain of *Candida albicans* is isolated.
- f. Treatment of PD catheter-related infection (exit site infection)
 - i. Oral therapy is generally appropriate when the patient is able to tolerate it.
 - ii. Treatment duration is a minimum of 2 weeks and at least 7 days after complete resolution of the infection. Infections caused by *S. aureus* or *Pseudomonas aeruginosa* should be treated for at least 3 weeks.
 - iii. If the infection is caused by MRSA, intraperitoneal or intravenous glycopeptide therapy is recommended for 2–4 weeks.

Table 7. Antibiotic Dosing Recommendations for the Treatment of Peritonitis

Antibiotic Type	Therapy Type		
	Continuous ^a		Intermittent ^a
	Loading Dose (mg/L)	Maintenance Dose (mg/L)	
Aminoglycoside (IP) ^b			
Gentamicin	8	4	Anuric: 0.6 mg/kg
Tobramycin	8	4	Non-anuric: 0.75 mg/kg
Amikacin	25	12	
Cephalosporins (IP)			
Cefazolin	500	125	20 mg/kg
Cefepime	500	125	15 mg/kg
Ceftazidime	500	125	20 mg/kg
Cefotaxime	500	250	30 mg/kg
Glycopeptides (IP) ^c			
Vancomycin	1000	25	30 mg/kg; repeat dosing 15 mg/kg every 3–5 days
Penicillins (IP) ^b			
Ampicillin		125	—
Quinolones (IP)			
Ciprofloxacin	50	25	—
Others			
Aztreonam (IP)	1000	250	—
Clindamycin (IP)	300	150	—

^aFor continuous therapy, the exchange with the loading dose should dwell for 3–6 hours; all subsequent exchanges during the treatment should contain the maintenance dose. For intermittent therapy, the dose should be applied once daily in the long dwell unless otherwise specified.

^bBecause of the potential for inactivation, aminoglycosides and penicillins should not be mixed in dialysis fluid.

^cIn patients with residual renal function, glycopeptide elimination may be accelerated.

IP = intraperitoneally.

Adapted from: Warady B, Bakkaloglu S, Newland J, et al. ISPD guidelines/recommendations: consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. *Perit Dial Int* 2012;32:pS50:Table 6.

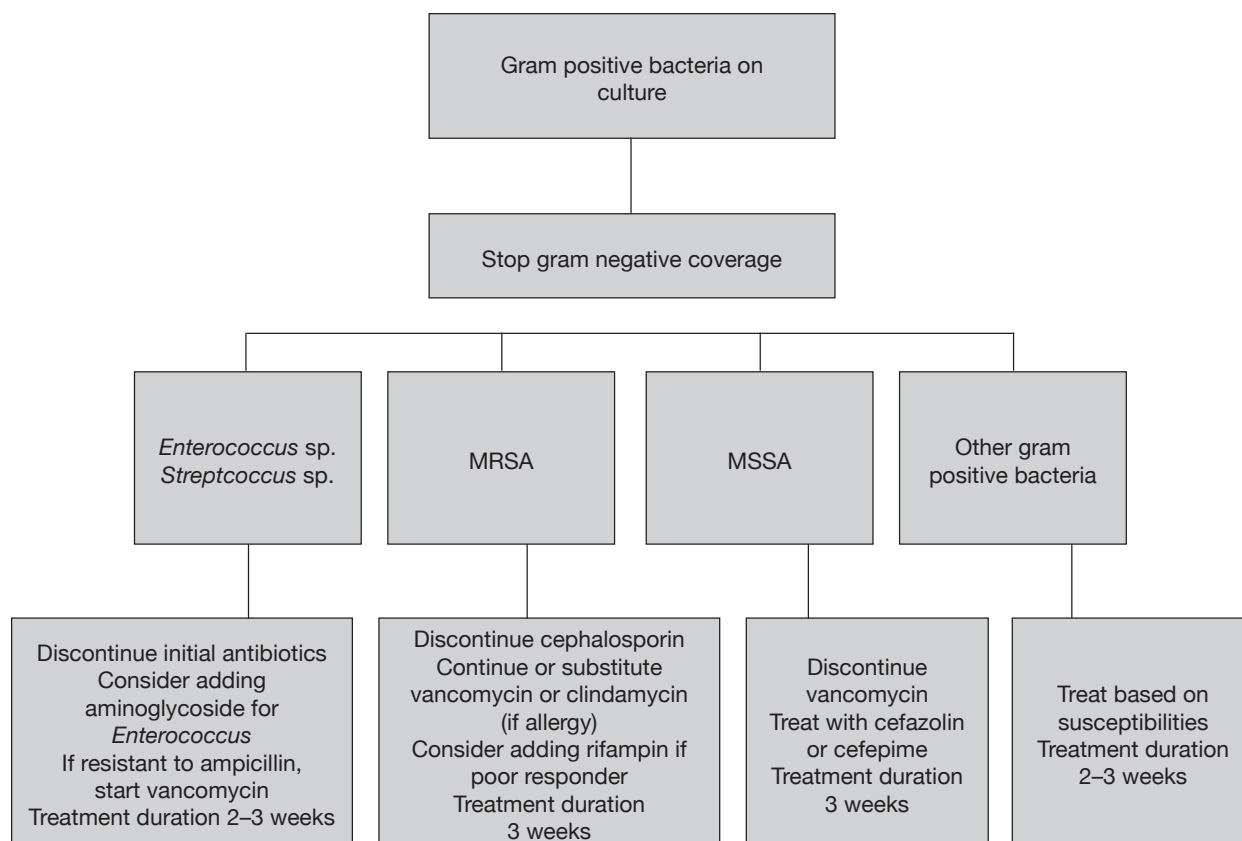


Figure 2. Culture-definitive gram-positive peritoneal dialysis catheter infection treatment.

Adapted from: Warady B, Bakkaloglu S, Newland J, et al. ISPD guidelines/recommendations: consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. *Perit Dial Int* 2012;32:pS54:Figure 2.

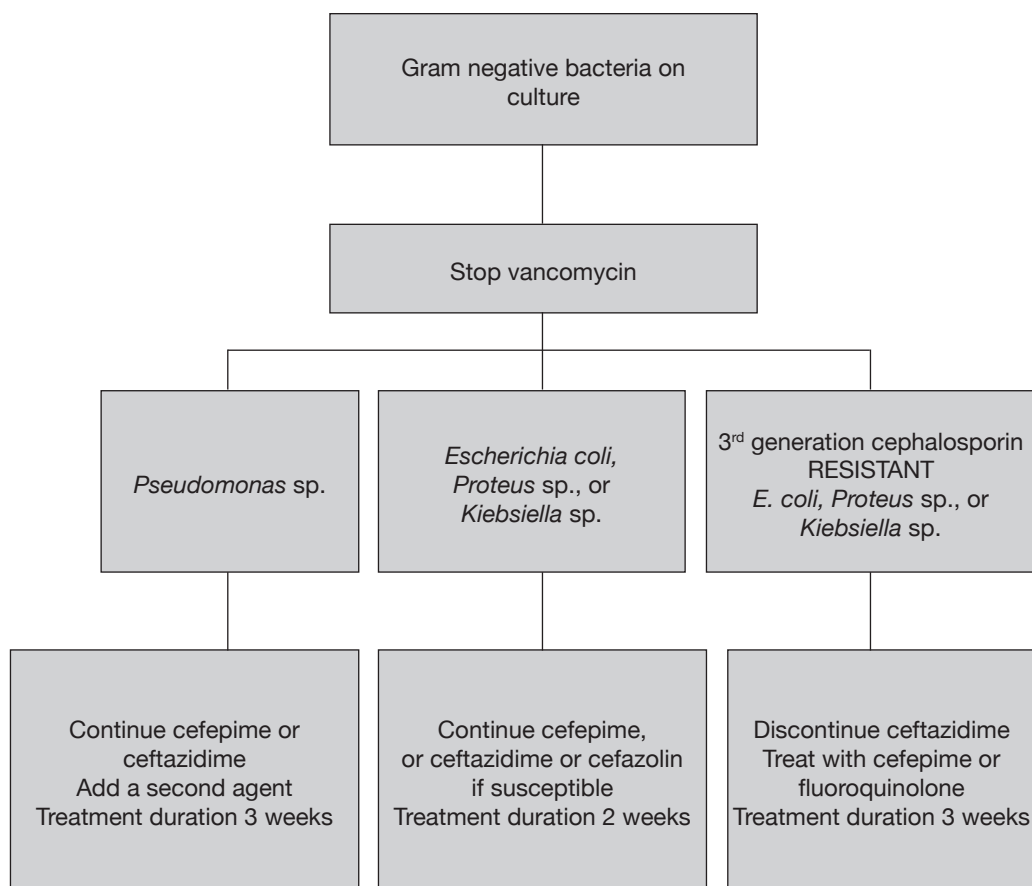


Figure 3. Culture-definitive gram-negative peritoneal dialysis catheter infection treatment.

Adapted from: Warady B, Bakkaloglu S, Newland J, et al. ISPD guidelines/recommendations: consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. *Perit Dial Int* 2012;32:pS56:Figure 3.

Patient Cases

Questions 10 and 11 pertain to the following case.

T.B. is a 2-month-old girl (weight 4.23 kg) with CKD caused by autosomal recessive polycystic kidney disease. She is being seen urgently in the nephrology clinic today because her mother reports increased fussiness, fever, and abdominal girth. The nephrologist notes that the peritoneal effluent is cloudy, and the fluid is sent for cell count, differential count, and culture. Because of her poor feeding and agitation, the infant is admitted to the inpatient unit for monitoring. This infant has a history of MRSA infection from a line while she was in the neonatal ICU. You note that she was released just 2 weeks ago from the neonatal ICU after a 6-week stay after birth.

10. Which empiric antibiotic regimen is the best empiric recommendation?
 - A. Vancomycin plus ceftazidime.
 - B. Cefazolin plus gentamicin.
 - C. Cefepime monotherapy.
 - D. Cefazolin plus ceftazidime.

11. Two days later, the effluent culture returns with *E. coli* that is resistant to third-generation cephalosporins. Which change to the current therapy would be best?
 - A. Continue previous regimen and add levofloxacin.
 - B. Discontinue all antibiotics and initiate gentamicin monotherapy.
 - C. Initiate cefepime monotherapy.
 - D. Change therapy to double coverage with meropenem and gentamicin.

VIII. HEMOLYTIC UREMIC SYNDROME

- A. Pathophysiology – A classic triad of features, including microangiopathic hemolytic anemia, thrombocytopenia, and AKI. Hemolytic uremic syndrome (HUS) is part of a broad category of diseases known as thrombotic microangiopathies.
 1. Typical HUS: More than 90% of HUS in children is attributed to a Shiga toxin–producing *E. coli* (*E. coli* O157:H7, also called STEC or diarrhea+ (D+)), which is typically characterized by acute, often bloody, diarrhea at the onset.
 - a. Pathogenic cascade starts with ingestion of STEC (usually infected meat but can also be found in vegetables, beverages/water). The *E. coli* O157:H7 strain is the most common, but there are many non–O157:H7-producing strains as well.
 - b. Ingestion of STEC causes colitis. The inflamed colon facilitates transmural absorption of Shiga toxins and lipopolysaccharides into the circulation.
 - c. Shiga toxins are then engaged by glycoprotein (gB3) receptors on target cells in the gut, kidney, and possibly other vital organs. Subsequent internalization leads to inhibition of protein production, which results in damage or death of the cells and detachment from their basement membranes.
 - d. Platelets are activated, as is the coagulation cascade. Platelets bind to Shiga toxin, further amplifying the prothrombotic state.
 - e. STEC is quite hardy and virulent. One survey found that active disease–producing STEC could survive in environments for up to 10 months after initial contamination.
 - f. The incidence rate of HUS differs by country and climate. Rates of typical HUS seem to be highest in colder climates.

2. Atypical HUS: Also known as “complement HUS” or diarrhea-negative (D-) HUS. May be associated with bone marrow transplantation, systemic lupus erythematosus, malignant hypertension, HIV infection, calcineurin inhibitors, cancer, *S. pneumoniae*, and other phenomena. Some authors have also attributed cases of HUS to drugs, including ticlopidine, clopidogrel, gemcitabine, L-asparaginase, and vincristine. Acute colitis may or may not be a presenting symptom in atypical HUS.
 - a. Mutations in the genes of complement components and regulators are one possible pathogenic feature of atypical HUS. Up to 12% of patients with atypical HUS have a combination of two or more mutations in components of complement.
 - b. There is also a familial atypical form of HUS, and the disease has an autosomal recessive or dominant pattern of inheritance.
 - c. Trigger events may play a role in atypical HUS, among them include upper respiratory infection, fever, varicella, H1N1 influenza, SARS-CoV-2, pregnancy, and diarrhea (event) plus a genetic predisposition to atypical HUS because of existing complement mutations.

B. Clinical Features and Diagnosis

1. Typical HUS

- a. The condition is usually diagnosed in children 6 months–4 years of age.
- b. Onset is preceded by a gastroenteritis, including vomiting, abdominal pain, and diarrhea that is watery at first and then becomes bloody. Fever may be present. Pallor, irritability, weakness, lethargy, and oliguria will begin 5–10 days after GI illness.
- c. Physical examination may reveal dehydration, edema, petechiae, hepatosplenomegaly, and irritability.
- d. This diagnosis is strongly suspected when the clinical triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure are found (after diarrheal illness).
 - i. The peripheral blood smear will show fragmented RBCs (schistocytes). Plasma hemoglobin concentrations will be high, but plasma haptoglobin concentrations will be low. The Coombs test will be negative. Leukocytosis may be significant and even exceed 30,000/mm³.
 - ii. Urinalysis may reveal hematuria and proteinuria.
 - iii. Coagulation studies are typically normal.
 - iv. Renal insufficiency can vary from mild to severe.
 - v. Colonoscopy will reveal spasm, as well as edema and thickening.
 - vi. Stool study (rectal swab) will have evidence of Shiga toxin–producing *E. coli*.

2. Atypical HUS

- a. Can occur in any age group, though disease is more severe in infants and young children. Less than 5% of typical HUS occurs in patients younger than 6 months of age, making onset at this age highly suggestive of atypical HUS.
- b. Initial symptoms may include pallor, irritability, poor feeding, vomiting, fatigue, drowsiness, edema, and diarrhea.
- c. Children with atypical HUS will have low C3/C4/C5 (complements) plasma concentrations in addition to the classic symptoms of microangiopathic hemolytic anemia, thrombocytopenia, and nephropathy, which are also found in typical HUS.
- d. In up to 60% of patients with aHUS, pathogenic mutations in complement (regulatory) genes, such as complement factor H (CFH), membrane cofactor protein (MCP), and C3, can be detected (Pediatr Nephrol 2019;34:2261-77). About 10% of patients, predominantly adolescents, have auto-antibodies directed against CFH (Mol Immunol 2015;67:31-42).

C. Treatment

1. Typical HUS is treated with supportive measures only. Supportive treatment can include:
 - a. Fluid and electrolyte management
 - b. Blood pressure management
 - c. Transfusion management should be cautious and conservative. There are few reports, but most authors suggest platelet or RBC transfusion only when absolutely necessary because the exposure to platelets or RBCs may worsen the thrombotic microangiopathy.
2. Antibiotics may be required when sepsis or lung infections complicate HUS, as in HUS associated with *S. pneumoniae* infection. Evidence about the role of antibiotics for the treatment of STEC is conflicting, with some studies reporting increased mortality when antibiotic therapy is used. In general, the decision to treat or not should be discussed and, if used, used with caution.
 - a. As with all infectious diarrheas, use of antidiarrheal and antispasmodics is not recommended and may worsen outcomes.
 - b. Renal replacement therapy will often be required. Citrate-based anticoagulation is preferred because there are theoretical concerns that heparin may cause HUS or worsen it.
 - c. The American Society for Apheresis recommends against therapeutic plasma exchange for the treatment of STEC HUS without severe neurological changes (J Clin Apher 2016;31:149-62).
 - d. Many clinicians believe eculizumab may play a role in the treatment of severe STEC HUS; however, randomized controlled trials are lacking.
 - e. Careful monitoring of neurologic status for rare but serious central nervous system involvement
 - f. Long-term follow-up is required because 30%–50% of children who survive typical HUS will go on to develop chronic renal impairment and/or hypertension.
3. Atypical HUS will require supportive treatment similar to that above, with some additional therapies, including:
 - a. Plasmatherapy
 - i. No trials evaluating the efficacy of plasmatherapy have been conducted. Despite this, plasma-therapy was considered first-line therapy for many years.
 - ii. Plasmatherapy will remove mutated complement proteins and complement antibodies, and with the use of fresh frozen plasma there is replacement of defective complements, including C3. If noninfectious HUS is suspected, emergent plasmatherapy should be considered while complement testing/genotype results are awaited, because irreversible renal lesions may develop early in the disease process.
 - iii. Response to plasma therapy varies depending on the affected complement component. In responders, daily plasma therapy continues until hemoglobin stabilizes, platelets normalize, and renal function has improved. At that time, plasma therapy may be progressively decreased over the span of 4–6 weeks.
 - iv. May aid in management of fluid overload
 - v. Plasma therapy modalities may remove medications, so dose adjustments or timing changes may be required when plasmatherapy is initiated.
 - vi. Risks associated with plasmatherapy include hypo- or hypertension, hypocalcemia, bleeding complications, catheter infections, and anaphylactic reactions to plasma.
 - b. Eculizumab
 - i. Recombinant humanized monoclonal IgG antibody that acts as a terminal complement inhibitor by binding C5 and blocking its cleavage to C5b, which is a proinflammatory peptide. It also prevents the generation of the cytotoxic membrane attack complex C5b-9
 - ii. FDA-indicated for the treatment of atypical HUS and has been studied in infants as young as 2 months
 - iii. Eculizumab is available only through a restricted program under REMS because of the risk of meningococcal disease. Under the Soliris REMS, prescribers must enroll in the program.

- iv. Dosing (see Table 8). Supplemental doses are required if the patient is undergoing plasmatherapy but not if the patient is undergoing dialysis. There is interest in the potential for therapeutic drug monitoring with eculizumab serum concentrations, but further studies are required.

Table 8. Eculizumab Dosing for Atypical Hemolytic Uremic Syndrome

Patient Body Weight	Induction	Maintenance
≥ 40 kg	900 mg weekly × 4 doses	1200 mg at week 5; then 1200 mg every 2 wk
30 kg to < 40 kg	600 mg weekly × 2 doses	900 mg at week 3; then 900 mg every 2 wk
20 kg to < 30 kg	600 mg weekly × 2 doses	600 mg at week 3; then 600 mg every 2 wk
10 kg to < 20 kg	600 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 2 wk
5 kg to < 10 kg	300 mg weekly × 1 dose	300 mg at week 2; then 300 mg every 3 wk

Soliris (eculizumab) [package insert]. Cheshire, CT: Alexion Pharmaceuticals, revised November 2020.

- v. May increase risk of infection, particularly with encapsulated organisms. The Advisory Committee on Immunization Practices (ACIP) recommends that all patients 2 months of age (though ACIP allows 6 weeks as the minimum age) or older receive the meningococcal vaccine at least 2 weeks before eculizumab is initiated. ACIP recommends that eculizumab recipients receive both quadrivalent meningococcal conjugate (MenACWY) and serogroup B (MenB) meningococcal vaccines. Pneumococcal vaccination is also recommended if the patient has not already received it.
- vi. Treatment with eculizumab is commonly started less than 2 weeks after meningococcal vaccination. The manufacturer and most centers strongly recommend antibiotic prophylaxis for meningococcal infection for at least 2 weeks after meningococcal vaccination. The most recent ACIP Meningococcal Vaccine update from 2020 suggests that because the risk of meningococcal meningitis is so high (a more than 2000-fold increase), providers may consider antibiotic prophylaxis throughout the duration of complement treatment even with appropriate vaccination (MMWR 2020;69:1-41).
- vii. Eculizumab recipients remain at risk for meningococcal disease even after receipt of meningococcal vaccines. Recently, ACIP reviewed several meningococcal infection cases in patients receiving eculizumab therapy who had received the MenACWY and MenB vaccines before eculizumab initiation. The group reviewed the risk of developing meningococcal disease in the United States as well as recommendations from outside the United States for continuous antibiotic prophylaxis during the entirety of eculizumab therapy and decided that antibiotic prophylaxis, with or without a safety or salvage option for an antibiotic supply to be kept at the patient's home in case of fever, was a reasonable recommendation (J Pediatric Infect Dis Soc 2017;6:311-6). The recommendation to use continuous antibiotic prophylaxis was echoed in a CDC report (MMWR Morb Mortal Wkly Rep 2017;66:734-7). If continuous antibiotic prophylaxis is used, the recommendation is for penicillin-based therapy, when possible, because of the known safety of long-term penicillin prophylaxis and the overall favorable susceptibility of *N. meningitidis* to penicillin in the United States. For patients with a penicillin allergy, azithromycin may be considered as an alternative.
- viii. Eculizumab is generally well tolerated, but patients should be monitored for infusion reactions, allergic reactions, hypertension, and new infection. Eculizumab is given over 35 minutes in adult patients (max 2 hours total), but it is recommended that it be given over 1–4 hours in pediatric patients. The infusion may be slowed or discontinued for adverse effects; however, if the infusion is slowed, the total infusion time should not exceed 2 hours in adults. The maximum infusion time is not stated in the package insert for children if infusion slowing occurs, but the presumption is that 4 hours will be the maximum duration.

- ix. Cost is a factor. The acquisition cost of Soliris is more than \$6000 per 300-mg vial. Some have estimated the yearly cost at greater than \$400,000, and therapy may be lifelong because there is no cure at this time for atypical HUS.
- c. Ravulizumab-cwvz
 - i. Ravulizumab-cwvz is a long-acting C5 inhibitor and is a modification of eculizumab. It requires less frequent administrations, which may be of particular benefit to school age children.
 - ii. Ravulizumab-cwvz is approved for adult and pediatric patients 1 month of age and older with aHUS.
 - iii. Ravulizumab-cwvz is available only through a restricted program under a REMS program. Providers who prescribe must be specifically certified and enrolled in the Ultomiris REMS program.
 - iv. Dosing (see Table 9): Though plasmapheresis (plasmapheresis, plasma exchange, or fresh frozen plasma administration) may reduce serum levels, at this time, the manufacturer does not have a recommendation for supplemental dosing. Also, therapeutic drug monitoring with ravulizumab-cwvz has not been explored.
 - v. Ravulizumab recipients are at high risk for meningococcal disease from any serogroup. The manufacturer recommends following ACIP recommendations (as given previously under eculizumab) for patients with complement deficiencies including revaccination during therapy. Patients without a history of meningococcal disease should receive meningococcal vaccination at least 2 weeks prior to receiving the first dose, or as soon as possible, and provide patients with 2 weeks of antibacterial drug prophylaxis.
 - vi. Administration of ravulizumab is generally well tolerated. The most common adverse events reported in premarketing trials included UTI, diarrhea, nausea, vomiting, headache, hypertension, and pyrexia. Infusion requires inline filtration with a 0.2 or 0.22 micron filter. The infusion rate is dose- and patient weight-dependent. Patients should be monitored for infusion-related reactions during the infusion and 1 hour after the infusion is complete.
 - vii. Cost remains a factor with ravulizumab; however, a U.S. cost-minimization model study has estimated significant cost reduction in comparison with eculizumab (J Med Econ 2020;1503-15).

Table 9. Ravulizumab-cwvz Weight-Based Dosing for Atypical Hemolytic Uremic Syndrome

Body Weight Range (kg)	Loading Dose (mg)	Maintenance Dose (mg)	Dosing Interval
5 to <10	600	300	Every 4 wk
10 to <20	600	600	
20 to <30	900	2100	Every 8 wk
30 to <40	1200	2700	
40 to <60	2400	3000	
60 to <100	2700	3300	
≥100	3000	3600	

Ultomiris (ravulizumab-cwvz) [package insert]. Cheshire, CT: Alexion Pharmaceuticals, revised June 2021.

Patient Case

12. T.T. is a 2-year-old girl (weight 14 kg) admitted to the pediatric ICU with GI symptoms for 7 days and now with new-onset hematochezia, diarrhea, fever, dehydration, and edema. She is awake and alert, and her vital signs are stable. Home medications included acetaminophen 200 mg by mouth every 6 hours as needed for fever and saline nasal drops as needed for congestion. The admission laboratory work shows WBC count 16×10^3 cells/mm³ with 56% segs, 12% bands, 27% lymphs, 3% eosinophils, 2% basos, hemoglobin 8 mg/dL, hematocrit 24.6, and platelet count 75,000/mm³; peripheral smear shows schistocytes, helmet cells, and polychromasia. Laboratory test results are: sodium 133 mEq/L, potassium 5.9 mEq/L, chloride 96 mEq/L, bicarbonate 16 mEq/L, BUN 45 mg/dL, creatinine 1.3 mg/dL, glucose 145 mg/dL, calcium 7.8 mg/dL, PO₄ 7.1 mg/dL, uric acid 7.3 mg/dL, and lactate dehydrogenase 300 IU/L. Coagulation and complement studies are normal. The stool sample is positive for *E. coli* O157:H7. Which clinical features best distinguish this patient as having typical HUS versus atypical HUS?
- The presence of hematochezia and previous upper respiratory infection.
 - Age plus hemolytic anemia, thrombocytopenia, and acute renal failure.
 - Hemolytic anemia, thrombocytopenia, and acute renal failure plus *E. coli* O157:H7.
 - Age, history of diarrheal symptoms, and findings of hematochezia plus STEC-positive stool and normal complement studies.

IX. TUBULOINTERSTITIAL NEPHRITIS

- Background
 - Immune-mediated cause of acute renal failure characterized by inflammatory infiltration of the cells in the interstitium of the kidney
 - TIN can be acute in onset or, in rare cases, chronic with a slow progression toward ESRD.
 - There is no standardized classification system. Some references further subcategorize TIN as infectious or non-infectious, depending on the purported origin. Others separate out drug-induced, infectious, systemic (disease state-related), and TIN with uveitis.
- Pathophysiology
 - Lymphocytic infiltration of the tubulointerstitium, tubular edema, and varying degrees of tubular damage. Fibrosis is often absent initially but may occur over time if treatment is delayed.
 - Eosinophils may be present in drug-induced TIN and may also form granulomas. Granuloma formation suggests a greater likelihood of infection-induced TIN as compared with drug-induced TIN.
 - Cause not fully understood but may be T-cell mediated
 - Progression to chronic TIN occurs with replacement of inflammatory cells with fibrosis. The interstitial tissue will have fibrosis and cellular infiltrates such as fibroblasts, T lymphocytes, and macrophages. CD8⁺ cells are the predominant lymphocytes crossing the basal tubule. Monocytes and macrophages will increase production of adhesive molecules that lead to fibrosis.
- Etiology
 - Can be drug induced. For a list of possible causative drugs, see Table 10.
 - Drugs may be a direct cause of TIN or can cause a hypersensitivity reaction that leads to TIN (NSAIDs are the classic example). Often there is a period between use of the offending drug and onset of TIN, varying from 5 days–5 weeks.

- b. Because of the anti-inflammatory properties of NSAIDs, some authors have described less proteinuria, absence of systemic eosinophilia, and less eosinophilic infiltrate on biopsy and a better clinical outcome from NSAID-induced TIN versus other medications.
 - c. Because drug-induced TIN is hypersensitivity based, the reaction is not related to the dosage that was used.
2. Infection is also believed to be a major cause of TIN. See Table 11 for a list of possible infectious causes.
3. Finally, certain disease states may be associated with the development of TIN, among them systemic lupus erythematosus, Sjögren syndrome, and Crohn disease.

Table 10. Drug Causes of Tubulointerstitial Nephritis

Antibiotics	Antivirals	Antiepileptic Drugs	Other
Penicillins	Acyclovir	Carbamazepine	Furosemide
Cephalosporins		Phenobarbital	Thiazides
Macrolides		Phenytoin	Allopurinol
Tetracyclines		Valproic acid	Azathioprine
Rifampin			Proton pump inhibitors
Ethambutol			NSAIDs
Isoniazid			Cyclosporine
Vancomycin			
Sulfamethoxazole/ trimethoprim			
Ciprofloxacin			

Table 11. Infectious Causes of Tubulointerstitial Nephritis

Viral Infections	Other
Adenovirus	Bacterial (<i>Salmonella</i> , <i>Streptococcus</i> , <i>Yersinia</i> , <i>Brucella</i> , and many others)
BK virus	Histoplasmosis
Cytomegalovirus	<i>Toxoplasma gondii</i>
Epstein-Barr virus	SARS-CoV-2
HIV	
Hepatitis B virus	

D. Clinical Manifestations

1. Signs and symptoms of TIN may be nonspecific and are often absent unless acute renal failure develops. Most children will have normal urine output, and some will have polyuria and nocturia with signs of tubular dysfunction.
2. About 20% of children with allergic interstitial nephritis will have a triad of symptoms: fever, eosinophilia, and allergic rash. Absence of these symptoms does not exclude a diagnosis of TIN.
3. Severity ranges from mild (minimal increase in urea concentrations with no symptoms) to severe (acute renal failure and decreased urine output). In patients with severe TIN, there may be tubular dysfunction with features of Fanconi syndrome.

E. Diagnosis

1. Investigation is usually symptom triggered, combined with confirmatory laboratory workup.
2. Urine analysis will have presence of eosinophils if TIN is immune-allergic in origin and minimal proteinuria (less than 0.5 g/24 hours) can be found; in rare cases, patients will present with nephrotic syndrome. The urine analysis may also reveal red or white blood cells.
3. Serum immunoglobulin E (IgE) may be high in about 50% of patients.
4. Renal ultrasonography may be normal, or it may reveal echogenic kidneys or an obstructive uropathy.
5. Vesicocytourethrography can detect VUR or bladder abnormalities.
6. Renal biopsy may necessary for diagnosis; symptoms may be present in only 20% of patients. Biopsy typically reveals eosinophilic infiltration of the renal parenchyma and normal glomeruli.

F. Treatment

1. Elimination of the offending drug agent, if possible
2. Supportive maintenance of fluid and electrolyte balance
3. Steroid therapy
 - a. At this time there has been no large-scale randomized or prospective trial evaluating steroids in the treatment of TIN. Because of the lack of prospective controlled trial evidence, particularly in children, therapy with steroids is still controversial.
 - b. A 2013 multicenter single-country (Finland) prospective study was conducted in 21 children younger than 17 years with a diagnosis of biopsy-proven TIN (Pediatr Nephrol 2013;28:1253-60). Children were to be randomized to receive prednisone or placebo. Children in the prednisone group received oral prednisone twice a day at a dose of 2 mg/kg/day (max 60 mg/day) for 1 month in 10-mg tablets. If full recovery was noted at the 4-week follow-up, the prednisone dose was reduced to 40 mg/m²/day every other day for 1 week and tapered thereafter by 10 mg/m² per dose in 1-week steps. If SCr or urine low-molecular-weight protein excretion was not normalized at 1 month, the prednisone dose was reduced to 1.5 mg/kg/day every other day for 2 months, followed by 1 mg/kg/day every other day for 1 month, followed by 0.5 mg/kg/day every other day for 1 month. Eleven children were in the prednisone group and six in the non-treatment group. They ranged in age from 5.4–16.9 years. Plasma creatinine began to normalize earlier in the prednisone-treated patients than in the non-treatment group. After 1 month, plasma creatinine had normalized in all patients in the prednisone group (n=11) and in three patients in the non-treatment group (n=6) (p=0.025). At the 6-month follow-up, plasma creatinine had decreased in all patient groups; however, it decreased significantly only in the prednisone group with a high baseline creatinine (baseline SCr greater than 1.7 mg/dL) (p<0.001). The authors believe that they confirmed previous retrospective findings supporting the assertion that prednisone accelerates the disappearance of renal symptoms in patients with TIN.
 - c. Other regimens from literature are variable and include the use of methylprednisolone intravenously 500–1000 mg/1.73 m²/day for 3 days, which is then changed to oral prednisone 0.5–2 mg/kg/day and tapered over 3–6 weeks of total therapy.
 - d. Mycophenolate mofetil, methotrexate, cyclosporine, and azathioprine have also been tried for non-responders to steroid therapy.

Patient Case

13. K.L. is a 10-year-old boy (weight 36 kg) admitted to the pediatric ICU on a Friday evening with community-acquired pneumonia and a high likelihood of MRSA infection, according to his medical history. He was started on vancomycin 720 mg (20 mg/kg) intravenously every 6 hours plus ceftriaxone 1 g intravenously every 24 hours for empiric coverage. A fourth-dose vancomycin trough concentration was in the goal range at 17.7 mcg/mL on Saturday. On Monday, the team notes on his daily basic metabolic panel that his SCr has increased to 1.4 mg/dL from his baseline of 0.5 mg/dL. You suspend his vancomycin therapy and obtain a trough before what would have been his next dose. The vancomycin trough is 34.2 mcg/mL. His nurse notes that his urine appears dark, and an emergency renal ultrasonography reveals echogenic kidneys. Urine analysis shows 1+ proteinuria and the presence of eosinophils. He is given a diagnosis of TIN caused by vancomycin. Which most accurately depicts the most appropriate antibiotic regimen with the lowest risk of TIN?
- A. Clindamycin 360 mg intravenously every 8 hours plus ceftriaxone 1 g intravenously every 24 hours.
 - B. Doxycycline 100 mg orally twice daily plus ceftriaxone 1 g intravenously every 24 hours.
 - C. Levofloxacin 360 mg intravenously every 24 hours.
 - D. Continue ceftriaxone 1 g intravenously every 24 hours as monotherapy.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: D

This patient presents to the ED with the classic symptoms of nephrotic syndrome, including hypoalbuminemia, hypoproteinemia, and high cholesterol. His rapid response and resolution of symptoms with 8 weeks of oral steroid therapy indicate MCNS, which accounts for 85% of all cases of nephrotic syndrome. Response within 8–12 weeks occurs in 95% of children with MCNS. This response would not be expected with the other forms of nephrotic syndrome, including membranous nephropathy, focal segmental glomerulosclerosis, and IgA nephropathy (Answer D is correct; Answers A–C are incorrect).

2. Answer: A

The Centers for Disease Control and Prevention does not recommend that live vaccines be administered to children who have been receiving corticosteroids at a dose equivalent to prednisone 2 mg/kg/day or greater for 14 or more days. Once steroids are discontinued, a 1-month wait before the administration of live vaccines is recommended. This patient has been off steroids for 4 months (Answer A is correct; Answer B is incorrect). There is no current recommendation to separate out vaccines in the childhood vaccination series for perceived optimization of immunity (Answer D is incorrect). A mild upper respiratory infection is not a contraindication to vaccination (Answer C is incorrect).

3. Answer: B

This patient appears to have had a good response to cyclosporine therapy with additional steroids. She has been in a prolonged remission and is experiencing steroid-driven adverse effects. At this time, a trial of steroid withdrawal would be appropriate to minimize adverse effects (Answer B is correct). Discontinuing cyclosporine would not address this patient's current physical and psychosocial issues (Answer A is incorrect). Further dietary modifications would likely yield little benefit, because the patient's mother has stated that the child already eats healthily, and it would not address the patient's insomnia (Answer C is incorrect). Switching from cyclosporine to tacrolimus would have minimal effect on the patient's weight gain, because weight gain is driven by the steroid exposure, not the calcineurin inhibitor (Answer D is incorrect).

4. Answer: A

Rituximab (Rituxan) is FDA labeled to be administered after pretreatment with acetaminophen and diphenhydramine to minimize the risk of infusion reaction (Answer C is incorrect). Rituximab has a black box warning stating the risk of fatal infusion reactions (Answer D is incorrect). Rituximab is not FDA indicated for the treatment of nephrotic syndrome, and using a corticosteroid as a premedication is not mandated. Most studies involving rituximab for the treatment of nephrotic syndrome have used pretreatment with intravenous methylprednisolone 30 minutes before the rituximab infusion. Pretreatment with methylprednisolone, acetaminophen, and diphenhydramine meets the rituximab package insert requirements and adds coverage, as extrapolated from other indications (Answer A is correct). Pretreatment with crystalloids may help prevent hypotension, but crystalloids are not formally recommended; their use should be reserved for patients who experience symptomatic hypotension during infusion (Answer B is incorrect).

5. Answer: A

The recommendation from a large meta-analysis published in 2013 was to use CAP in patients with high-grade hydronephrosis; however, the meta-analysis was based on low-quality evidence. In 2014 a pilot study and randomized placebo-controlled trial (RIVUR) compared children with hydronephrosis and VUR, respectively, treated with sulfamethoxazole/trimethoprim suspension with placebo. The authors found that the risk of febrile or symptomatic recurrence of UTI was reduced among children who received prophylaxis compared with those who received placebo (Answer C is incorrect). Despite this finding, cost-effectiveness and decision analysis studies are needed to further clarify the role of antimicrobial prophylaxis. The nephrologist has already chosen to initiate therapy on the basis of the evidence available. The best choice would be to start therapy with the agent that has the most objective data supporting it (Answer A is correct). Amoxicillin has not been studied in a controlled manner for the prevention of UTI in hydronephrosis or VUR, and the consensus prophylactic dosing recommended is lower than that presented (Answer B is incorrect). The relative risk of antibiotic therapy has not been adequately clarified to state that it is unsafe. Antimicrobial resistance is a concern, but it has not been well studied (Answer D is incorrect).

6. Answer: A

Plasma anion gap is calculated as $[\text{Serum sodium}] - ([\text{Serum bicarbonate}] + [\text{Chloride}])$, or $[136 \text{ mEq/L}] - ([13 \text{ mEq/L}] + [111 \text{ mEq/L}]) = 12 \text{ mEq/L}$ (Answer A is correct; Answers B–D are incorrect).

7. Answer: B

This patient has the classic symptoms of type 4 RTA, including hyponatremia and hyperkalemia, with a plasma bicarbonate of 15 mEq/L or greater and a mild decrease in GFR. Treatment with sodium bicarbonate alone may help correct the acid–base imbalance in the short term but does not address the underlying cause, which is aldosterone deficiency or resistance. Lowering the infant's potassium concentration is a long-term solution, but it would not help in the ED setting (Answer A is incorrect). Intravenous sodium chloride may help replace sodium and fluid deficit but will likely not fully correct the patient's hyperkalemia (Answer C is incorrect). Spironolactone may exacerbate hyperkalemia and hyponatremia because spironolactone is an aldosterone blocker that competes with aldosterone for receptor sites in the distal renal tubule (Answer D is incorrect). Furosemide will lower potassium in the ED setting (Answer B is correct).

8. Answer: D

The AKIN criteria have been studied and shown to be clinically useful in infants undergoing cardiac surgery, but these criteria rely on SCr and urine output (Answer A is incorrect). The RIFLE criteria (as opposed to the pRIFLE criteria) are intended for adult patients but also depend on a combination of GFR and urine output (Answer B is incorrect). Serum BUN in newborns is not considered accurate, given that it can be high because of many factors in newborns in addition to renal dysfunction (Answer C is incorrect). Serum cystatin C is the most helpful estimate of renal function in a newborn of the provided choices because it can distinguish maternal creatinine from newborn creatinine, even in the first few days of life (Answer D is correct).

9. Answer: C

This patient has a high iPTH (1100 pg/dL), which increases his risk of renal osteodystrophy, and high serum phosphorus and serum calcium concentrations. He is already taking a large dose of calcium acetate and has a high calcium phosphorus product of $74 \text{ mg}^2/\text{dL}^2$ (goal less than $55 \text{ mg}^2/\text{dL}^2$). Increasing the calcium acetate dose may not

add much benefit and may further increase his risk of calcium deposition in soft tissue (Answer A is incorrect). Ergocalciferol may be beneficial for this patient, but because of his ESRD, he may be unable to properly convert ergocalciferol to activated vitamin D, which could worsen his hypercalcemia (Answer B is incorrect). A change to sevelamer would not address the significantly increased iPTH (Answer D is incorrect). The correct choice would be to change him to a non–calcium-based phosphorus binder such as sevelamer and add cinacalcet to lower iPTH (Answer C is correct). Cinacalcet has not been studied in pediatric patients, but for this patient, who is 16 years old and weighs 82 kg, it would be appropriate. However, because of the recent clinical hold on cinacalcet, it would be prudent to alert caregivers to the risks and benefits associated with cinacalcet therapy and ensure proper monitoring.

10. Answer: A

The ISPD guidelines recommend initial empiric therapy for PD patients with cloudy effluent while culture results are awaited. The guidelines state that cefepime monotherapy is the first-line recommendation. However, in this case cefepime monotherapy is not appropriate because of the patient's history of MRSA (Answer C is incorrect). A second-line choice is a first-generation cephalosporin combined with either ceftazidime or an aminoglycoside. However, this option is inappropriate for this patient because it lacks MRSA coverage (Answers B and D are incorrect). A glycopeptide should be added to cefepime, or it should replace the first-generation cephalosporin if the patient has a history of MRSA infection (Answer A is correct). However, some centers may choose coverage with vancomycin plus cefepime or vancomycin plus an aminoglycoside instead.

11. Answer: C

Following the ISPD guidelines for PD infections, coverage may be narrowed once the bacterium is known. When the organism is gram-negative, the guidelines recommend discontinuation of vancomycin (Answer A is incorrect). For *E. coli*, *Proteus* spp., or *Klebsiella* spp., the guidelines recommend 2 weeks of cefepime, cefazolin, or ceftazidime, depending on susceptibilities. Discontinuing all antibiotics and initiating gentamicin monotherapy is incorrect; monotherapy with aminoglycosides is not recommended under the guidelines (Answer B is incorrect). Double coverage is not

necessary for *E. coli* and is not recommended by the guidelines (Answer D is incorrect). Cefepime monotherapy is the best choice for single coverage of *E. coli* (Answer C is correct).

12. Answer: D

Diagnosis of typical HUS depends predominantly on the presence of stool positive with Shiga toxin–producing *E. coli* O157:H7 or other non-O157 *E. coli* strains. Patients will also have the classic triad of symptoms, including hematochezia, thrombocytopenia, and acute renal failure, though these symptoms do not distinguish typical from atypical HUS, because both forms have them (Answers A and B are incorrect). Although hemolytic anemia, thrombocytopenia, and acute renal failure plus *E. coli* O157:H7 describe the characteristics of typical HUS, they do not distinguish it from atypical HUS (Answer C is incorrect). The presence of normal coagulation studies separates atypical from typical HUS. Although it is possible for a patient to have atypical HUS in the presence of *E. coli* O157:H7–positive stools, typical HUS is ruled out if the complement studies are normal (Answer D is correct).

13. Answer: A

In the setting of acute TIN for a patient who was concomitantly exposed to both vancomycin and a cephalosporin, which are known to cause TIN, the clinician must use judgment when deciding how to alter the regimen to address ongoing infectious coverage while removing a possible offending agent. In this example, Answers B and C are incorrect; Answer B adds a drug that is on the possible TIN list, which might further exacerbate the problem, and Answer C does not address the concern regarding MRSA coverage. Answer D is incorrect because, like Answer C, it does not cover MRSA. Answer A is correct because it introduces a drug that is not implicated in TIN but that also covers MRSA, which will allow the clinician to further distinguish whether vancomycin or ceftriaxone caused the TIN.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: A

Enalapril 0.2–0.6 mg/kg/day decreases proteinuria in children with steroid-dependent nephrotic syndrome (Answer A is correct). β -Blockers and calcium channel blockers will not prevent proteinuria, and they have not been studied in children with nephrotic syndrome (Answers B and C are incorrect). The starting dose of lisinopril given is likely too aggressive (Answer D is incorrect).

2. Answer: B

The 2021 KDIGO guidelines recommend several monitoring parameters for patients receiving rituximab therapy including baseline hepatitis B surface antigen (Answer B is correct), hepatitis B core antibody, and a QuantiFERON tuberculosis test (Answer D, a purified protein derivative or purified protein derivative skin test is incorrect). The QuantiFERON test is more reliable and therefore preferred. Whereas baseline creatinine measurement may be a part of other monitoring being done, is it not recommended by KDIGO (Answer A is incorrect). Live vaccines should be avoided before and during treatment; however, a varicella titer is not recommended by KDIGO at this time (Answer C is incorrect).

3. Answer: D

The risk of UTI increases with increasing grade of hydronephrosis and peaks at 40% in children with grade IV hydronephrosis. Antibiotic prophylaxis remains controversial. Epidemiologically focused studies have weakly recommended that children with mild hydronephrosis receive no prophylaxis, whereas children with more severe disease may benefit (Answers A and C are incorrect). Vesicoureteric reflux occurs in 10%–20% of children with antenatal hydronephrosis; however, a 1-day-old boy with antenatal hydronephrosis now with neonatal oliguria has not yet been confirmed to have VUR (Answer B is incorrect). Many had hoped that the RIVUR study would answer these questions definitively; however, the authors drew no strong conclusions regarding the role of antimicrobial prophylaxis in children with VUR; instead, they stated that their data supported reduced recurrence in treated children. If antibiotic prophylaxis is necessary, a 6-week-old girl with antenatal hydronephrosis now with voiding cystourethrography showing grade IV VUR would be expected to reap the most benefit, according to a 2013

meta-analysis showing that children with high-grade hydronephrosis who received prophylaxis had a significantly lower UTI rate than those not receiving prophylaxis (Answer D is correct).

4. Answer: B

Live vaccinations for children with nephrotic syndrome should be deferred until their prednisone dose is less than 2 mg/kg/day (max 20 mg) for 1 month after the completion of therapy with cytotoxic agents, such as cyclophosphamide, and for 1 month after the completion of other daily immunosuppression, such as cyclosporine. In this example, the pediatrician should be comfortable giving all the vaccines (live and inactivated), because the patient takes only 1 mg/kg prednisone every other day, making Answer B correct and Answers A, C, and D incorrect.

5. Answer: D

Hydrochlorothiazide and spironolactone are not recommended as first-line treatments for distal RTA (Answers A and B are incorrect). Sodium bicarbonate could be used; however, there is a risk of promoting hypercalciuria because of increased sodium intake, which could increase the risk of renal calculi, and this infant already has nephrocalcinosis (Answer C is incorrect). The first-line therapy for distal RTA is potassium citrate, and the usual starting dose is 2–4 mEq/kg/day, which corrects urinary abnormalities while minimizing the risk of calcium oxalate stones (Answer D is correct).

6. Answer: C

This question asked for the modified Schwartz equation calculation, which is as follows:

$$\text{CrCl (mL/minute/1.73 m}^2\text{)} = 0.413 \times L \text{ (cm)}/\text{SCr}$$

where L is length in centimeters. For this case, the calculation would be set up as follows:

$$\text{CrCl (mL/min/1.73 m}^2\text{)} = 0.413 \times (36 \text{ in} \times 2.54 \text{ in/cm})/0.7 \text{ mg/dL} = \text{mL/min/1.73 m}^2$$

According to this equation, Answer C is correct, and Answers A, B, and D are incorrect.

7. Answer: B

A switch to calcium acetate might increase adherence if that is a problem, but it would not address the high calcium phosphorus product (Answer A is incorrect). No serum albumin is provided; however, CKD serum albumin is typically normal or low. The adjusted equation for calcium that is based on albumin would only yield a higher calcium value, which would still require a change in therapy, because the calcium phosphorus product would still be increased beyond $65 \text{ mg}^2/\text{dL}^2$ (Answer C is incorrect). Decreasing the calcium carbonate daily dose would address the patient's high serum calcium concentration but would not address the high serum phosphorus (Answer D is incorrect). The calcium phosphorus product is high for this patient, and avoiding a calcium-based phosphate binder is recommended (Answer B is correct).

8. Answer: A

Calcitriol is an optimal choice in this infant because of his chronic hepatorenal dysfunction. He has both hypovitaminosis D, which would be corrected by the ergocalciferol, and an increased iPTH, which would be corrected by the calcitriol. (Answer A is correct). It is unlikely that ergocalciferol alone would correct his high iPTH (Answer B is incorrect). Paricalcitol is currently available only in capsule form, and there is not yet an FDA indication for children. In addition, there is only limited study information for pediatric patients (Answer C is incorrect). Cholecalciferol may be an option if this patient's insurance does not cover calcitriol or the family cannot afford it, but it remains less than optimal because it still requires renal activation for function and would not correct the iPTH (Answer D is incorrect).

9. Answer: D

The *Nelson Textbook of Pediatrics* is a good reference, but it contains no referenced drug-dosing recommendations (Answer A is incorrect). The KDIGO guidelines do not address the dosing of drugs in PD (Answer B is incorrect). Epocrates does not provide references for its dosing recommendations, so you might feel uncomfortable using it (Answer C is incorrect). A good place to begin when dosing an antibiotic for PD is the ISPD guidelines. They contain not only dosing recommendations for antibiotics for PD infection but also information about admixture into PD solutions, which may be required as well (Answer D is correct). Although

not a provided answer choice, primary literature may be required to find the most up-to-date information, because tertiary references and guidelines may not capture recent publications.

10. Answer: C

This child likely has many health care exposures because of her oncology diagnosis. She may have a permanent indwelling central line in addition to her PD catheter for chemotherapy, and she is likely at high risk for MRSA infection (Answer C is correct). Intraperitoneal cefepime at a 125-mg/L loading dose is incorrect; it assumes that she has no risk factors for MRSA (Answer A is incorrect). Delaying antibiotics while waiting for culture results is not recommended in the ISPD guidelines for patients with cloudy PD effluent and is likely inappropriate for a presumed immunocompromised patient (Answer D is incorrect). Neither cefazolin nor an aminoglycoside will address her health care exposure-related risk factors (Answer B is incorrect).

11. Answer: C

Although a pamidronate infusion may address the serum calcium concentration, it is unclear whether it is truly necessary in this patient. There are few data on pamidronate use in pediatric patients with stage 4 or 5 CKD, and the benefit may not outweigh the risk (Answer A is incorrect). Shortening the dwell time for PD exchanges will increase the degree of ultrafiltration and urea removal, but typically it will not increase the removal of phosphorus and will not address mildly increased serum calcium concentrations (Answer B is incorrect). The simplest solution would be to change the PD formulation to one that contains a lower amount of calcium and repeat the electrolyte analysis in 1–2 weeks (Answer C is correct). Increasing the frequency of PD exchanges may increase solute clearance, but a greater proportion of the time is spent draining and filling, and it may be less effective than using a larger dwell volume (if possible, depending on patient size) (Answer D is incorrect).

12. Answer: A

The classic symptoms of typical HUS (STEC) are described in the case, though there are not yet any stool studies to confirm it. Eculizumab is not indicated for typical HUS at this time (Answer A is correct). Although eculizumab therapy is quite expensive, many

still consider it the first-line therapy for atypical HUS (Answer B is incorrect). Eculizumab increases the risk of meningococcal infection; therefore vaccination with or without antibiotic coverage during treatment is recommended. However, eculizumab has not been associated with worsening of the underlying STEC in patients with typical HUS who have received eculizumab (case reports) (Answer C is incorrect). Eculizumab is a recombinant antibody with a molecular weight of 148 kDa. Although studies examining the effect of CRRT on eculizumab removal have not been conducted, there is currently no recommendation for alternation in dosing, except in patients undergoing plasmatherapy. Therefore it is not expected that significant removal would occur in the setting of CRRT (Answer D is incorrect).

13. Answer: B

Although it is believed that eculizumab increases the risk of infection of all types, the only formal recommendation to date is to ensure meningococcal vaccination before initiating eculizumab (Answer B is correct; Answers A, C, and D are incorrect).

14. Answer: C

Although both azithromycin and clarithromycin cover group A *Streptococcus*, they have both been associated with the development of TIN (Answers A and D are incorrect). Only clindamycin is not a possible cause of TIN, and it is therefore the safest drug to prescribe to complete therapy in a patient with acute TIN (Answer C is correct). Cefuroxime lacks adequate coverage against group A *Streptococcus*, and cephalosporins have been implicated in TIN (Answer B is incorrect).

NEUROLOGY/PSYCHIATRY

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Learning Objectives

1. Apply evidence-based medication therapy for acute and prophylactic treatment of migraines.
2. Distinguish between seizure medications by type of seizure, age, drug interactions, and adverse effects.
3. Differentiate between the medication therapies for cerebral palsy symptoms of spasticity, drooling, bone mineral density loss, sleep, and pain control.
4. Evaluate between the medications for autism spectrum disorders for target symptoms and adverse effects.
5. Select appropriate medication therapy and monitoring values for pediatric bipolar disorder according to symptoms, bipolar phase, and adverse events.
6. Develop treatment plans for attention-deficit/hyperactivity disorder, including medication recommendations, adverse events, and dosage formulations.
7. Identify treatment options and potential adverse effects of medications for pediatric depression.

Abbreviations in This Chapter

ADHD	Attention-deficit/hyperactivity disorder
ASD	Autism spectrum disorder
CBT	Cognitive behavior therapy
ED	Emergency department
EEG	Electroencephalogram
GABA	γ -Aminobutyric acid
RCT	Randomized controlled trial
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant

Self-Assessment Questions

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

1. R.H. is a 15-year-old female adolescent who presents to the emergency department (ED) with a headache. She describes her headache as a throbbing, pulsing pain in the front of her head. Bright lights seem to worsen the pain. She has been nauseated since the headache began and has vomited twice in the past hour. Which medication is best, given R.H.'s symptoms?
 - A. Almotriptan oral tablet.
 - B. Hydrocodone/acetaminophen oral tablet.
 - C. Hydromorphone intravenous injection.
 - D. Sumatriptan nasal spray.
2. S.K. is a 5-year-old girl (weight 20 kg) with focal (partial onset) seizures. She was initiated on carbamazepine 2 months ago. For the first month after the dose was titrated to 200 mg twice daily, she had no seizures. After the first month, however, the seizures recurred. A therapeutic concentration of 3.5 mg/mL (normal range 4–12 mg/mL) was obtained. Which is the most likely reason the concentration is below normal range?
 - A. Carbamazepine binds to protein binding.
 - B. Carbamazepine has displacement of the free fraction.
 - C. Carbamazepine is an autoinducer.
 - D. Carbamazepine has multi-phasal distribution.
3. C.F. is a 12-year-old boy (weight 45 kg) who has been having difficulty in school. He has been described as staring off into space and not paying attention. He seems to do this many times a day, but each episode lasts for only a few seconds. Which is the best medication for C.F.?
 - A. Ethosuximide.
 - B. Topiramate.
 - C. Phenobarbital.
 - D. Phenytoin.
4. M.M. is an 8-year-old boy with cerebral palsy. His primary symptoms are muscle tightness in his arm, a scissored gait, grimacing in his face, and an intermittent tremor. His mother brings a prescription for baclofen 5 mg every 8 hours. Which best reflects the target symptom in M.M. for which baclofen has been prescribed?
 - A. Ataxia.
 - B. Athetoid movements.
 - C. Dyskinesia movements.
 - D. Spasticity.
5. M.P. is an 11-year-old boy with autism disorder. His current symptoms include an inability to communicate verbally, inability to follow directions,

irritability, self-injurious behavior, flat affect, and aggression. He often gets upset, and if his routine is disrupted, he starts rocking back and forth. Aripiprazole is prescribed. Which symptom is aripiprazole most likely to improve?

- A. Poor verbal communication.
- B. Irritability.
- C. Flat affect.
- D. Inability to follow directions.

Questions 6 and 7 pertain to the following case.

T.E. is a 15-year-old female adolescent with bipolar disorder. She presents with an expansive mood, grandiosity, and flight of ideas. She has not slept for more than 2 hours for at least 1 week. Her parents brought her to the hospital because she was communicating with her online boyfriend and told him she would wire him \$10,000.

- 6. Which would be the most appropriate medication for T.E.?
 - A. Olanzapine.
 - B. Lamotrigine.
 - C. Fluoxetine.
 - D. Methylphenidate.
- 7. The physician would like to prescribe lithium for T.E. For which adverse effect is lithium most likely titrated with initiation?
 - A. Leukopenia.
 - B. Nausea/vomiting.
 - C. Pancreatitis.
 - D. Early jitteriness and anxiety.
- 8. K.C. is a 14-year-old male adolescent (weight 45 kg) who presents to the ED with hallucinations, paranoia, and aggression. Medication reconciliation shows that the dose of his attention-deficit/hyperactivity disorder (ADHD) medication was recently doubled. Of the medications indicated to treat ADHD, which is most likely causing K.C.'s symptoms?
 - A. Atomoxetine.
 - B. Clonidine XR.
 - C. Guanfacine XR.
 - D. Methylphenidate.

- 9. N.B. is a 12 year girl who was given a diagnosis of ADHD. The physician prescribed atomoxetine. Which of the following is the most likely adverse event to occur with atomoxetine?

- A. Gastrointestinal (GI) discomfort.
- B. Hallucinations.
- C. Hypotension.
- D. Increased appetite.

Questions 10 and 11 pertain to the following case.

K.B. is a 13-year-old female adolescent who presents with depressed mood, insomnia, weight loss, feelings of guilt, and suicidal ideation. She has felt this way for the past 3 months. Several weeks ago, she almost tried to overdose on her mother's oxycodone but then confessed her thoughts to her mother. At that time, she was admitted to the hospital, but no medications were prescribed. The current presentation began when she notified her mother of her suicidal thoughts, and her mother brought her immediately to the hospital for evaluation. This time, the physician would like to initiate an antidepressant.

- 10. Which medication is best for K.B.?

- A. Venlafaxine.
- B. Duloxetine.
- C. Escitalopram.
- D. Amitriptyline.

- 11. K.B. was stabilized at the hospital and discharged home with a prescription of an antidepressant. After doing well with her medication for 1 year, K.B. did not think she needed it any longer and abruptly stopped taking it. Two days later, her depression came back, and she felt worse than before. She had 2 nights of vivid dreams, felt that someone was trying to shock her, and had severe nausea. Which is most likely occurring?

- A. Rebound depression.
- B. Serotonin syndrome.
- C. Serotonin discontinuation syndrome.
- D. Onset of manic symptoms.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5

I. MIGRAINES/HEADACHES**A. Epidemiology**

1. Headache
 - a. Prevalence for all children and adolescents younger than 20 years is estimated at 58.4% worldwide.
 - b. Prevalence female-to-male ratio is 1.5/1 for all children and adolescents younger than 20.
2. Migraine
 - a. Prevalence for all children and adolescents younger than 20 is estimated at 7.7%.
 - b. Prevalence for females is 9.7% and for males, 6%.
 - c. Prevalence of migraines is the same for females as for males younger than 14, and migraines are more prevalent in adolescent females.
3. Abdominal migraine accounts for 4%–15% of chronic, recurrent abdominal pain.
4. Cluster headaches are rare in children younger than 10 years.
5. Comorbid conditions such as seizures and psychiatric diagnoses are common with headache and migraine.

B. Classifications of Headache by the International Headache Society

1. Migraine without aura
 - a. At least five attacks of headache lasting 2–72 hours with at least two of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, aggravating or causing avoidance of routine physical activity.
 - b. During the headache, at least one of the following: nausea and/or vomiting, photophobia, phonophobia.
 - c. Occipital headache in children is rare, and migraine headaches in general are usually frontotemporal.
 - d. In young children, photophobia and phonophobia may be inferred from their behavior.
 - e. Migraine is more often bilateral in children and adolescents. Unilateral pain emerges in late adolescent or early adult life.
2. Migraine with aura (sensation, as of lights or warm/cold air currents)
 - a. At least two attacks with one or more fully reversible aura symptoms and at least three of the following
 - i. At least one aura symptom for more than 4 minutes
 - ii. Two or more symptoms occurring in succession
 - iii. No single aura symptom lasts more than 60 minutes
 - iv. Headache follows aura within 60 minutes
 - v. One aura symptom is unilateral
 - vi. One aura symptom is positive (scintillations [flashes of lights] and pins and needles)
 - b. Typical auras consist of visual, sensory, or speech symptoms. Examples include flickering lights or spots, feeling of pins or needles, and numbness.
3. Episodic syndromes are commonly precursors of migraine.
 - a. Cyclic vomiting: At least five attacks of intense nausea and vomiting lasting from 1 hour to 10 days; vomiting during attacks occurs at least four times per hour for at least 1 hour, attacks occur more than 1 week apart, and child is symptom free between attacks (see GI chapter)
 - b. Abdominal migraine
 - i. At least five attacks that last 2–72 hours with abdominal pain that is midline, periumbilical, or poorly localized
 - ii. Dull or “just sore” quality
 - iii. Moderate to severe intensity.
 - c. For the abdominal pain attack criteria, at least two of the following must occur: anorexia, nausea, vomiting, or pallor.

- d. Benign paroxysmal vertigo
 - i. At least five attacks of vertigo occurring without warning and resolving spontaneously after minutes to hours, together with a normal neurologic examination and normal electroencephalogram (EEG).
 - ii. At least one sign or symptom of nystagmus, ataxia, vomiting, pallor, or fearfulness is associated with benign paroxysmal vertigo.
- e. Benign paroxysmal torticollis
 - i. Recurrent attacks with onset in the first year of life.
 - ii. Attacks are a tilt of the head to either side, with or without slight rotation, remitting spontaneously after minutes to days.
 - iii. At least one sign or symptom of pallor, irritability, malaise, vomiting, or ataxia is associated with benign paroxysmal torticollis.
 - iv. Ataxia is more likely in older children.
- 4. TTH (tension-type headache)
 - a. At least 10 previous headaches, each lasting from 30 minutes to 7 days, with no nausea and vomiting and no more than one headache with photophobia and phonophobia
 - b. With at least two of the following: pressing/tightening (nonpulsating) quality; mild to moderate intensity; bilateral location; no aggravation with physical activity
- 5. Treatment of Pediatric Migraine
- 6. Practice guidelines updated in 2019 for children and adolescents for acute and prophylactic treatment
- 7. Acute treatment
 - a. Goals are rapid response resulting in a prompt return to normal activity, no relapse, and minimal adverse effects.
 - b. Patient counseling should include information about migraine health habits, lifestyle modification, migraine triggers, aggravating factors, and avoidance of medication overuse.
 - c. Acute treatments are more likely to be effective earlier in the migraine attack when the pain is still mild.
 - d. Ibuprofen (Motrin, Advil) has been studied and is effective.
 - i. Recommended as initial treatment to reduce pain for children and adolescents.
 - e. Acetaminophen (Tylenol) is also listed in the guidelines as a treatment option.
 - i. Ibuprofen was more efficacious than acetaminophen and lasted longer, but both medications were well tolerated.
 - f. Triptans (5-hydroxytryptamine_{1D}-receptor agonists) (Table 1)
 - i. Almotriptan oral tablet (12–17 years old), rizatriptan oral tablet and orally disintegrating tablet (6–17 years old), zolmitriptan nasal spray (12–17 years old), and sumatriptan/naproxen oral tablet (12–17 years old) are the only FDA label-approved treatment for pediatric migraine.
 - ii. Sumatriptan nasal spray, zolmitriptan oral tablet and orally disintegrating tablet, rizatriptan oral tablet and orally disintegrating tablet, and eletriptan have all been studied in the adolescent population with some positive results.
 - iii. Sumatriptan subcutaneously has positive open-label data with doses of 3–6 mg (0.06 mg/kg/dose) for those 6–18 years of age. The oral formulation of sumatriptan was not statistically significantly different from placebo.
 - iv. For adolescents, the practice parameter recommends sumatriptan/naproxen, sumatriptan nasal spray, zolmitriptan nasal spray, rizatriptan orally disintegrating tablet, or almotriptan.
 - v. Naratriptan and frovatriptan have no efficacy studies for this population.

Table 1. Summary of Triptans Investigated for Pediatric Migraine

Generic Name	Brand Name	Dosage Form	Time to Relief (hr)	Indication
Almotriptan	Axert	Tablets	2	FDA label approved for migraine in 12- to 17-yr-old adolescents
Eletriptan	Relpax	Tablets	2	Studies show reduction in recurrent migraine in 12- to 17-yr-old adolescents NOT FDA label approved
Rizatriptan	Maxalt Maxalt MLT	Tablets, ODT	2	FDA label approved for migraine in 6- to 17-yr-old adolescents
Sumatriptan	Imitrex	Nasal spray	2	12- to 17-yr-old adolescents NOT FDA label approved
Sumatriptan	Imitrex	Subcutaneous injection	2	Open-label studies with mixed efficacy in 6- to 18-yr-olds NOT FDA label approved
Sumatriptan/ naproxen	Treximet	Tablet	2	FDA label approved for migraine in 12- to 17-yr-old adolescents
Zolmitriptan	Zomig	Tablets, ODT	2	Studies with mixed results of efficacy in 12- to 17-yr-old adolescents NOT FDA label approved
Zolmitriptan	Zomig	Nasal spray	2	FDA label approved for migraine in 12- to 17-yr-old adolescents

ODT = orally disintegrating tablet.

- g. Treatment with prochlorperazine is more effective than treatment with ketorolac.
- h. Other antiemetics such as promethazine, metoclopramide, and ondansetron have been used for treatment and for nausea/vomiting associated with migraines.
- i. If nausea and vomiting are present, non-oral formulations should be tried first (e.g., injectable or nasal).
- j. Although studies have found that opioids are commonly used for abortive migraine treatment in practice, guidelines advise against using these agents to treat migraine.
 - i. Reasons against using opioids for migraine: Increased risk of abuse, increased risk of chronic daily headache or medication overuse headache, lack of evidence supporting superior efficacy and hyperalgesia
- k. Dihydroergotamine has been used for treatment-resistant migraine, but it is not mentioned in the guidelines. Ergots have not been studied in children. Mechanism of action: An ergot alkaloid α -adrenergic blocker directly stimulates vascular smooth muscle to vasoconstrict peripheral and cerebral vessels; may also affect serotonin receptors
- l. Valproic acid
 - i. A retrospective chart review and retrospective case series found reduced pain scores.
 - ii. In adolescents, doses were 500–1000 mg intravenously for one or two doses. Valproic acid was not mentioned in the acute treatment guideline.
- m. Magnesium sulfate: One retrospective chart review found that magnesium 30 mg/kg (2000 mg max) infused over 30 minutes decreased pain scores. The dose can be repeated in 2 hours if magnesium concentrations are acceptable. Magnesium sulfate was not mentioned in the acute treatment guideline.
- n. For treatment-resistant migraine, intravenous fluids may be used for potential dehydration caused by prolonged vomiting.
- o. Intravenous steroids have been used for treatment-resistant migraine, but studies show no reduction in migraine recurrence after use.

8. Prophylactic treatment of pediatric migraine
 - a. General principles
 - i. Consider when headache frequency exceeds three or four episodes per month for at least 3 months or if headaches interfere with school or normal activities.
 - ii. Goals are to reduce the frequency, severity, and duration of attacks; improve responsiveness to treatment of acute attacks; improve function and quality of life; and reduce disability.
 - iii. Counseling to avoid risk factors associated with recurrent headache in adolescents should occur. These risk factors include being overweight, caffeine and alcohol use, lack of physical activity, poor sleep habits, tobacco exposure.
 - iv. No treatment has been approved by the FDA.
 - v. In placebo-controlled clinical trials for the prevention of pediatric migraine, many children and adolescents who received placebo improved; most preventive medications were not superior to placebo.
 - b. Medications with studies showing the efficacy of prophylaxis and included in guidelines:
 - i. Amitriptyline combined with cognitive behavior therapy (CBT)
 - (a) One study found no difference from placebo for reducing migraine headache when used alone.
 - (b) Adverse events include arrhythmias, weight gain, anticholinergic effects, daytime sedation, and potential for overdose.
 - (c) Doses are based on studies of children 6–12 years of age.
 - ii. Topiramate
 - (a) Studies comparing topiramate with placebo for reducing migraine headache favor topiramate, though one study showed no difference from placebo.
 - (b) Adverse effects include anorexia, weight reduction, gastroenteritis, paresthesia, somnolence, and dulled cognition.
 - (c) Doses above 200 mg decrease the effectiveness of oral contraceptives.
 - (d) FDA label approved preventive treatment of migraine in patients 12 years and older.
 - iii. Propranolol
 - (a) Studies comparing propranolol with placebo for reducing migraine headache favor propranolol.
 - (b) Adverse effects include bradycardia, hypotension, syncope, dizziness, drowsiness, and wheezing.
 - (c) Contraindicated in asthma
 - c. Other medications studied in pediatric patients with less evidence (see seizure section for adverse events)
 - i. OnabotulinumtoxinA – Mixed results in studies; one double-blind, placebo-controlled study showed improvement in chronic migraine and good tolerability
 - ii. Calcitonin gene-related peptide antagonists: FDA label approved in adults only; currently studied in pediatric patients, but results are pending
 - iii. Cyproheptadine – Insufficient evidence
 - iv. Valproic acid – Insufficient evidence for migraine prevention; not as well tolerated as other options
 - d. Alternative therapies
 - i. Magnesium has been studied in pediatric patients; may reduce the frequency of headaches, but patients tend to have GI adverse effects.
 - ii. Butterbur, coenzyme Q10, ginkgolide B, polyunsaturated fatty acids like fish oil, palmitoylethanolamide, and riboflavin all had potential efficacy in studies of pediatric patients; however, most studies had quality problems.
 - iii. Nonpharmacologic treatment: Evidence is good for CBT for treatment and as adjunctive treatment to medications. The ketogenic diet has been studied for migraine, but evidence is insufficient for efficacy.

Patient Cases

Questions 1 and 2 pertain to the following case.

A.M. is a 12-year-old girl (weight 50 kg) with a throbbing headache in the front of her head that has lasted 2 hours. She has phonophobia, but not nausea and vomiting. She describes this as the worst headache she has ever had. She has had “bad” headaches in the past, when acetaminophen has worked, but this headache was unrelieved with a 650-mg dose.

1. Which would be the next best step for her headache?
 - A. Ibuprofen orally.
 - B. Prochlorperazine orally.
 - C. Sumatriptan orally.
 - D. Topiramate orally.
2. After a few months, A.M. continues to have migraine headaches, consisting of about four per month. She has missed 1 week of school in the past month because of her migraines. Although the medications for acute treatment seem to be working, her mother is concerned about the amount of medications A.M. is taking and wonders whether A.M. could take something for migraine prevention. Which scheduled medication would be best for migraine prophylaxis?
 - A. Ibuprofen orally.
 - B. Prochlorperazine orally.
 - C. Sumatriptan orally.
 - D. Topiramate orally.
3. A.K. is a 6-year-old boy who comes to the ED with nausea, vomiting, irritability, and restlessness and states that his head hurts. When asked where it hurts, he says “all over my head.” His mother states he has been acting like this for several hours. She tried acetaminophen several hours ago, but his behavior and complaints did not appear to change. Which medication would best be tried next in A.K.?
 - A. Morphine intravenously.
 - B. Almotriptan orally.
 - C. Sumatriptan nasal spray.
 - D. Valproic acid orally.

II. SEIZURE DISORDERS (CHRONIC MANAGEMENT)**A. Epidemiology**

1. The estimated lifetime prevalence of childhood seizure disorders in the United States is 10 per 1000, or 1%.
2. About 10% of people in the United States will have a seizure.
3. Febrile seizures are the most common type of seizure in children age 6 months through 5 years, with a peak onset at 14–18 months of age.

B. Seizure Classifications

1. The International League Against Epilepsy (ILAE) determines the classification of seizures. The most recent update was published in 2017.

2. Focal (formerly partial): Seizures begin in one hemisphere of the brain and may have the following subsequent descriptors:
 - a. Aware of self and environment (simple partial seizure)
 - b. Impaired awareness at any part of the seizure (complex partial seizure)
 - c. Motor onset reflecting first sign or symptom at onset (automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, tonic)
 - i. Automatisms: Coordinated motor activity, usually amnesic afterward
 - ii. Hyperkinetic: Agitated thrashing or leg pedaling movements
 - iii. See Generalized Seizure Onset section for the definitions of other descriptors.
 - d. Nonmotor onset reflecting first sign or symptoms at onset
 - i. Autonomic: A distinct alteration of the autonomic nervous system function
 - ii. Behavior arrest: A pause of activities, freezing, or immobilization
 - iii. Cognitive: Pertaining to thinking and higher cortical functions, previously psychic seizures
 - iv. Emotional: Seizures present with emotions such as fear or joy
 - v. Sensory: A perceptual experience not caused by appropriate stimuli in the external world
 - e. Evolving to a bilateral tonic-clonic seizure (corresponds with secondarily generalized seizures)
3. Generalized seizure onset begins in both hemispheres of the brain.
 - a. Motor onset
 - i. Myoclonic: Brief, lightning-like jerking movements of the entire body or the extremities
 - ii. Tonic: Flexion and/or extension phases of tonic-clonic. Tonic is a sustained contraction of muscles with progressive rigidity.
 - iii. Clonic: Rhythmic, repetitive, jerking muscle movements
 - iv. Tonic-clonic: Pattern of first the flexion, the extension phase, and then the tremor and clonic phase. A postictal phase may occur in which the patient is difficult to arouse and/or is somnolent or confused.
 - v. Atonic: Loss of muscle tone. This may be described as a drop attack.
 - vi. Epileptic spasms (formerly infantile spasms): Spasmodic clusters of jerking contractions of the extremities, head, and trunk. West syndrome is a disorder with infantile spasms, an abnormal EEG pattern called hypsarrhythmia, and developmental delay. The new classification system changed the terminology because spasms can last beyond infancy.
 - vii. Myoclonic-tonic-clonic: One or two jerks of limbs bilaterally, followed by a tonic-clonic seizure. Common in juvenile myoclonic epilepsy (a.k.a. Janz syndrome)
 - viii. Myoclonic-atonic: A myoclonic jerk followed by an atonic motor component
 - b. Nonmotor (absence):
 - i. Typical: Brief and abrupt, lasts 10–30 seconds, occurs in clusters. May have a short loss of consciousness or the patient may stare into space
 - ii. Atypical: Changes in tone are more pronounced than in typical, and onset/cessation is not abrupt.
 - iii. Myoclonic: A rhythmic three-per-second myoclonic movement causing ratcheting in upper limbs leading to progressive arm elevation
 - iv. Eyelid myoclonus; jerking of the eyelids at frequencies of at least 3 per second, commonly with upward eye deviation, usually lasting less than 10 seconds, often precipitated by eye closure
4. Unknown onset
 - a. Motor onset (tonic-clonic, epileptic spasms)
 - b. Nonmotor onset (behavior arrest)
 - c. Unclassified

5. Epilepsies and syndromes
 - a. Lennox-Gastaut syndrome is a mixture of intractable seizures and absence seizures.
 - b. Benign epilepsy with centrotemporal spikes: Unilateral movements that occur in the sleep. The seizures are usually benign, and the child outgrows them.
 - c. Juvenile myoclonic epilepsy (a.k.a. Janz syndrome): Myoclonic jerks on awakening but patient may also have tonic-clonic seizures or absence seizures
 - d. Febrile seizures: A seizure that is accompanied by a temperature of 100.4°F (38°C) in children 6 months to 5 years of age without a diagnosis of central nervous system (CNS) infection. The seizures are related to the rate in rise in temperature, not the peak degree.
- C. Laboratory Data
 1. EEG can help determine the type of seizure and locate the site of the seizure, thereby directing the type of medication.
 2. MRI (magnetic resonance imaging) and CT (computed tomography) may help identify structural abnormalities.
- D. Anticonvulsant Treatments
 1. Guideline recommendations
 - a. American Academy of Neurology and the American Epilepsy Foundation level B (probably effective) recommendations
 - i. Ethosuximide and valproate should be tried before lamotrigine for decreasing seizure frequency for childhood absence seizures.
 - ii. Levetiracetam (1 month – 16 years), zonisamide (6–17 years), and oxcarbazepine (1 month – 17 years) should be considered to decrease seizure frequency for treatment-resistant focal epilepsy.
 - iii. Levetiracetam and lamotrigine should be considered as add-on therapy to decrease seizure frequency for treatment-resistant generalized tonic-clonic seizures.
 - iv. Levetiracetam should be considered as add-on therapy to decrease seizure frequency for treatment-resistant juvenile myoclonic epilepsy.
 - v. Clobazam should be considered as add-on therapy to decrease seizure frequency for Lennox-Gastaut syndrome.
 - b. American Academy of Neurology and American Epilepsy Foundation level A (established efficacy) recommendations
 - i. Rufinamide should be considered established as effective add-on therapy for Lennox-Gastaut syndrome.
 - c. The ILAE recommendations reviewed the literature in 2013.

Table 2. ILAE Summary of Medications for Infants with Seizures

Type of Seizure	Established	Probable	Possible	Ineffective
Focal	Levetiracetam			Topiramate Lamotrigine Gabapentin Oxcarbazepine
Generalized			Levetiracetam Valproic acid Lamotrigine Topiramate Clobazam	
Epileptic spasms		Adrenocorticotrophic hormone (ACTH)	Prednisone Vigabatrin	
Benign myoclonic epilepsy of infancy			Topiramate Valproic acid Lamotrigine Clonazepam	
Benign infantile spasms			Carbamazepine Phenobarbital Valproic acid	

Table 3. ILAE Summary of Medications for Types of Seizures in Children

Type of Seizure	Established	Possible/Probable	Potential
Partial	Oxcarbazepine	Carbamazepine Phenobarbital Phenytoin Topiramate Valproic acid Vigabatrin	Clobazam Clonazepam Lamotrigine Zonisamide
Generalized tonic-clonic		Carbamazepine Phenobarbital Phenytoin Topiramate Valproic acid	Oxcarbazepine
Absence	Ethosuximide Valproic acid	Lamotrigine	
Benign epilepsy with centrotemporal spikes		Carbamazepine Valproic acid	Gabapentin Levetiracetam Oxcarbazepine
Juvenile myoclonic epilepsy			Topiramate Valproic acid

Table 4. Medications for Children and Adolescents with Seizures

Medications	Mechanism of Action	Pharmacokinetics Dose Adjustments	Adverse Effects	Other Considerations
Brivaracetam	Interacts with synaptic vesicle protein 2A (SV2A) in the brain and affects neurotransmitter release	Metabolized by CYP2C19	Somnolence Dizziness Fatigue	Schedule V
Cannabidiol (Epidiolex)	Unknown Appears to work on cannabinoid receptors	High fat/high calorie increases absorption	Sedation Elevated LFTs Angioedema Erythema Pruritus	Drug interactions with valproic acid and clobazam
Carbamazepine	Inhibits voltage-gated sodium channels	Enzyme inducer Autoinducer Therapeutic concentrations: 4–12 mg/mL	Blurred vision Diplopia Ataxia Nausea Fatigue Dizziness Thrombocytopenia Leukopenia SIADH Hyponatremia Metabolic bone disease	Black box warning: Rash and dermatologic reactions that can be fatal; progression to Stevens-Johnson syndrome or toxic epidermal necrolysis Aplastic anemia Agranulocytosis
Cenobamate	Inhibits voltage-gated sodium channels; allosteric modulator GABA _A ion channels	Metabolized by CYP2E1, CYP2A6, and CYP2B6	QT shortening Hyperkalemia Dizziness Drowsiness Fatigue Headache Diplopia	No studies in children or adolescents
Clobazam	Benzodiazepine; augments (GABA _A) chloride influx	Avoid abrupt discontinuation	Somnolence Sedation Drooling Aggression Fatigue Irritability	Tolerability may develop Withdrawal symptoms include seizures, hallucinations, tremors, insomnia Schedule IV
Eslicarbazepine	Inhibits voltage-gated sodium channels Prodrug metabolized to eslicarbazepine, the active metabolite of oxcarbazepine	CYP3A4 inducer	Dizziness Drowsiness Blurred vision Headache Nausea Cognitive dysfunction	

Table 4. Medications for Children and Adolescents with Seizures (*continued*)

Medications	Mechanism of Action	Pharmacokinetics Dose Adjustments	Adverse Effects	Other Considerations
Ethosuximide	Inhibits T-type calcium channels	Therapeutic concentrations: 40–100 mcg/mL	Nausea/Vomiting Headache Drowsiness Fatigue Ataxia Leukopenia Eosinophilia Rash Behavior changes	
Everolimus	Reduced protein synthesis and cell proliferation by binding to the FK binding protein-12 that inhibits activation of mTOR serine-threonine kinase activity	Close therapeutic drug monitoring required Target trough concentration 5–15 ng/mL	Hypertension Peripheral edema Diabetes mellitus Abdominal pain Constipation Diarrhea Infections Anemia Leukopenia Fatigue Headache (side effects from transplant studies)	Only Afinitor Disperz indicated for treatment of tuberous sclerosis complex associated partial-onset seizures
Felbamate	Inhibits sodium channels, enhances GABA, inhibits NMDA receptors		Anorexia Somnolence Insomnia Nausea/vomiting Weight loss Gait abnormality	Black box warning: Aplastic anemia, acute hepatic failure Only for severe or refractory cases when other medications have failed
Fenfluramine	Serotonin transport inhibitor; serotonin 5-HT ₂ agonist	Metabolized by CYP1A2, CYP2B6, CYP2D6	Aortic insufficiency Hypertension Weight loss Decreased appetite Diarrhea Drowsiness Fatigue Drooling Asthenia Fever	For Dravet syndrome
Fosphenytoin	Prodrug for phenytoin	(see phenytoin)	(see phenytoin)	Parenteral formulation causes less hypotension, less risk of extravasation

Table 4. Medications for Children and Adolescents with Seizures (*continued*)

Medications	Mechanism of Action	Pharmacokinetics Dose Adjustments	Adverse Effects	Other Considerations
Gabapentin	Inhibition of the $\alpha_2\delta$ subunit of voltage-dependent calcium channels Increases GABA concentrations and synthesis Modulates sodium and calcium channels Inhibits monoamine neurotransmitter release	Saturable absorption Not metabolized Eliminated renally For 12 years and older, adjust dose when creatinine clearance is less than 60 mL/minute/1.73 m ²	Somnolence Fatigue Aggressive behavior Dizziness Weight gain	
Lacosamide	Inhibits slow sodium channels	Adjust dose when creatinine clearance is less than 30 mL/minute/1.73 m ²	PR-interval prolongation Dizziness Headache Diplopia Nausea/vomiting	Schedule V
Lamotrigine	Inhibits voltage-dependent sodium channels, decreases glutamate release	Titrate slowly to minimize risk of rash progression When given with valproic acid, the maximum dose is reduced to half of the recommended dose when given as monotherapy When given with inducers, maximum dose is twice that of recommended dose when given as monotherapy	Drowsiness Diplopia Dizziness Headache Confusion	Black box warning: Rash can progress to Stevens-Johnson syndrome and toxic epidermal necrolysis; most common in pediatrics within first 8 wk of treatment or when given with valproic acid
Levetiracetam	Interacts with SV2A protein to affect neurotransmitter release; facilitates GABA transmission	Minimally metabolized; adjust for renal dysfunction	Dizziness Somnolence Behavior/personality changes Irritability Hostility/aggression Nervousness Headache Hallucinations	Includes indication for myoclonic seizures with juvenile myoclonic epilepsy

Table 4. Medications for Children and Adolescents with Seizures (*continued*)

Medications	Mechanism of Action	Pharmacokinetics Dose Adjustments	Adverse Effects	Other Considerations
Oxcarbazepine	Inhibits sodium voltage-gated channels Prodrug that converts to the metabolite 10-monohydroxy oxcarbazepine; enzyme inducer	Therapeutic concentrations: 10–40 mcg/mL	Hyponatremia Rash Dizziness Drowsiness Nausea	
Perampanel	Inhibits AMPA glutamate subtype receptor	Long half-life, about 105 hr	Dizziness Fatigue Gait disturbances Somnolence Aggression/behavior changes Psychosis	Schedule III
Phenobarbital	Increases GABA chloride influx	Pan-enzyme inducer Long half-life and renal elimination in the neonate Therapeutic concentrations: 15–40 mcg/mL	Hyperactivity Cognitive impairment Drowsiness Lethargy Depression Respiratory depression with rapid intravenous administration	Schedule IV
Phenytoin	Block voltage-gated sodium channels	Enzyme inducer Nonlinear metabolism (Michaelis-Menten saturable metabolism) Therapeutic concentrations: 10–20 mcg/mL; free phenytoin: 1–2.5 mcg/mL	Nystagmus Ataxia Drowsiness Cognitive impairment Gingival hyperplasia Hirsutism Acne Rash Hepatotoxicity Rash	Administer intravenously slow
Pregabalin	Inhibition of the α_2 δ subunit of voltage-dependent calcium channels	Not metabolized Reduce dose in renal dysfunction	Drowsiness Ataxia Somnolence Weight gain Headache Blurred Vision	Schedule V
Rufinamide	Inhibits fast sodium channels	Absorption increased by food Administer with food Valproic acid increases rufinamide concentrations	Somnolence Dizziness Fatigue Nausea Headache Shortened QT interval	Indicated for Lennox-gastaut syndrome

Table 4. Medications for Children and Adolescents with Seizures (*continued*)

Medications	Mechanism of Action	Pharmacokinetics Dose Adjustments	Adverse Effects	Other Considerations
Stiripentol	Partial agonism and modulator of GABA _A ; inhibits CYP enzymes and increases concentrations of other anticonvulsants	CYP1A2 and CYP2C19 inhibitor	Drowsiness Agitation Ataxia Hypotonia Dysarthria Insomnia Weight loss Decreased appetite Nausea Thrombocytopenia Neutropenia Tremor	FDA approved in combination with clobazam Limited data for Dravet syndrome
Tiagabine	Inhibits GABA reuptake		Dizziness Nervousness Fatigue Depressed mood Concentration difficulties	May cause nonconvulsive status epilepticus
Topiramate	Inhibits fast sodium channels; enhances GABA and blocks AMPA glutamate subtype	Metabolized and renally eliminated	Drowsiness Paresthesias Weight loss Renal stones Metabolic acidosis Decreased sweating Concentration and memory difficulties Behavior problems Acute angle-closure glaucoma	
Valproic acid	Blocks T-type calcium channels, blocks sodium channels, increases GABA activity	Enzyme inhibitor Nonlinear protein binding Carbapenems decrease valproic acid blood concentrations; avoid use Therapeutic concentrations: 50–100 mcg/mL Divalproex capsules may be opened and sprinkled on food; do not chew sprinkles	Nausea/vomiting Weight gain Thrombocytopenia Alopecia Tremor Hyperammonemia	Black box warning: Hepatotoxicity (greater risk in children younger than 2 years); risk of acute liver failure in patients with mitochondrial disease; teratogenic effects; pancreatitis

Table 4. Medications for Children and Adolescents with Seizures (*continued*)

Medications	Mechanism of Action	Pharmacokinetics Dose Adjustments	Adverse Effects	Other Considerations
Vigabatrin	Irreversible inhibition of GABA transaminase	Renally eliminated	Fatigue Somnolence Nystagmus Tremor Blurred vision Weight gain Arthralgia Ataxia Confusion	Black box warning: Vision loss; may be permanent Obtain through Risk Evaluation and Mitigation Strategies (REMS) program
Zonisamide	Inhibits fast sodium channels; inhibits T-type calcium channels, weak carbonic anhydrase inhibitor		Somnolence Dizziness Decreased sweating Hyperthermia Metabolic acidosis Anorexia Rash Stevens-Johnson syndrome Nephrolithiasis Renal stones	

AMPA = α -amino-3-hydroxy-5-methyl-4-isoxazolepropionate; GABA = γ -Aminobutyric acid; LFT = liver function test; NMDA = N-methyl-D-aspartate; SIADH = syndrome of inappropriate antidiuretic hormone secretion.

2. Nonpharmacologic treatment

- Ketogenic diet:** Diet consisting of low-protein and low-carbohydrate and high-fat meals. May reduce seizure frequency in refractory cases. Medications, especially chewable tablets and liquids, often contain hidden carbohydrates, which can significantly impact the success of the ketogenic diet. Avoid medications that competitively interfere with fatty acid metabolism (e.g., valproic acid), cause metabolic acidosis (e.g., acetazolamide, topiramate, zonisamide), or dextrose-containing intravenous additives. Long-term adverse effects include weight loss, hyperlipidemia, hypoproteinemia, nephrolithiasis, renal tubular acidosis, constipation, growth retardation, and increases in hepatic and pancreatic enzymes. Monitor for QT prolongation and poor nutritional status.
- Vagal nerve stimulation:** Used as adjunctive therapy in refractory epilepsy
- Surgery:** Used for refractory focal seizures

3. Monitoring for suicidal behavior and ideation

- Class warning/precaution:** 2008 FDA advisory added a warning about increased risk of suicidal thoughts or actions for antiepileptic drugs with long-term use.
- All patients should be monitored for changes in suicidal thinking, changes in suicidal behavior, and depression.

Patient Cases

Questions 4 and 5 pertain to the following case.

A.P. is a 13-year-old male adolescent (weight 55 kg) initiated on oxcarbazepine monotherapy for focal seizures. His mother comes to the pharmacy to fill the prescription. The laboratory test result shows that the therapeutic concentration is 5 mcg/mL, and his mother asks what this means. The dose for the past month was 200 mg twice daily, and the new prescription is for the same dose. A.P.'s mother reports that he continues to have seizures, but only once in a while.

4. Which best explains the laboratory result?
 - A. Dose should be increased.
 - B. No change in dose is needed.
 - C. Dose should be decreased.
 - D. Another medication should be added.
5. A.P.'s mother has heard that antiepileptics have many adverse effects. Which adverse effect would the mother best be cautioned about regarding oxcarbazepine in A.P.?
 - A. Gingival hyperplasia.
 - B. Hirsutism.
 - C. Hyponatremia.
 - D. Renal failure.
6. K.W. is a 15-year-old female adolescent (weight 54 kg) with generalized tonic-clonic seizures. She has been taking valproic acid 125 mg four times daily. Her serum concentration is 80 mcg/mL. She is still having seizures, but the family does not want to increase the dose because, on higher doses, K.W. becomes very drowsy, uncoordinated, and lethargic. The physician would like to add lamotrigine. Which would be the best initial dose of lamotrigine for K.W.?
 - A. Administer one-half of the usual recommended starting dose.
 - B. Administer the usual recommended starting dose.
 - C. Administer twice the recommended starting dose.
 - D. Lamotrigine and valproic acid are contraindicated together.
7. Which best reflects the lamotrigine adverse effect correlated with speed of titration?
 - A. Rash.
 - B. Tremor.
 - C. Weight gain.
 - D. Thrombocytopenia.

Patient Cases (*continued*)

8. E.E. is a 16-year-old male adolescent who has been prescribed topiramate for juvenile myoclonic epilepsy. Which adverse event is most commonly associated with topiramate and is the one about which E.E. be counseled?
 - A. Tremor.
 - B. Rash.
 - C. Weight gain.
 - D. Memory/concentration difficulties.
9. N.P. is a 12-month-old girl who was brought to the ED after having a seizure in the evening. She has reportedly not been feeling well and is irritable, crying, and restless. Her mother thought she was sick and checked her temperature earlier in the morning. She reports that N.P.'s temperature was normal. Now, N.P.'s temperature is 102.4°F (39.1°C). The seizure lasted less than 1 minute. Which type of seizure does N.P. most likely have?
 - A. New-onset focal seizures.
 - B. New-onset generalized seizures.
 - C. Absence seizures.
 - D. Febrile seizures.

III. CEREBRAL PALSY

- A. Epidemiology
 1. Prevalence is two or three cases per 1000 in children.
 2. Ratio of boys to girls is 1.4:1.
- B. Gross Motor Function Classification System
 1. Level I: Walks without restriction: Limitations with more advanced gross motor skills
 2. Level II: Walks without assistive devices: Limitations to walking outdoors and in the community
 3. Level III: Walks with assistive devices: Limitations to walking outdoors and in the community
 4. Level IV: Self-mobility with limitations: Children are transported, or they use power mobility outdoors and in the community.
 5. Level V: Self-mobility is severely limited, even with the use of assistive technology.
- C. Classified by Type of Muscle Abnormality
 1. Spasticity
 - a. Stiff or tight muscles
 - b. Increased deep tendon reflexes
 - c. Scissored gait with toe-walking
 - d. Unilateral or bilateral
 - e. Upper and lower extremities may be affected.
 2. Dyskinesia (dystonic or athetoid)
 - a. Slow, uncontrollable writhing movements
 - b. Grimacing or drooling caused by hyperactive muscles of the face and tongue
 - c. Usually all four extremities

3. Ataxia
 - a. Unsteady wide-based gait
 - b. Intention tremor
 - c. Difficulty with precise motions such as writing
 - d. Usually all four extremities
 4. Hypotonia
 - a. Low muscle tone usually in all four extremities; “floppy muscles”
 - b. Excessive flexibility
 - c. Difficulty with stability
 - d. Developmental delays
- D. Treatment
1. Spasticity
 - a. Baclofen (oral)
 - i. Mechanism of action: GABA agonist. Binds to GABA_B receptors in the spinal cord
 - ii. Pharmacokinetics: Rapidly absorbed, metabolized in the liver
 - iii. Adverse events: Sedation, confusion. If abruptly discontinued, may cause withdrawal symptoms, including spasms, hallucinations, confusion, fever, and seizures
 - iv. Special considerations: If discontinuation is warranted, taper the dose.
 - b. Baclofen (intrathecal)
 - i. Indicated when other oral medications have failed (oral baclofen, other muscle relaxants, and botulinum toxin A), the patient is adherent to the office visits, and the patient is older than 4 years
 - ii. Administered by implantable pump with a continuous infusion. Pump is refilled by health care provider every 2–6 months.
 - iii. Overdose symptoms: Hypotonia, drowsiness, unarousability, respiratory depression
 - iv. Monitor for infections around the pump area or meningitis as well as for signs of pump malfunctions or blockage.
 - v. Abrupt withdrawal symptoms include elevated temperature, paresthesias, altered mental status, rebound spasticity, and muscle rigidity. In rare cases, it can progress to rhabdomyolysis, malignant hyperthermia, multiple organ system failure, and death.
 - c. Dantrolene
 - i. Mechanism of action: Inhibits the release of calcium at the sarcoplasmic reticulum, resulting in muscle weakness. Directly affects the skeletal muscles
 - ii. Adverse events: Drowsiness, irritability, hepatotoxicity, and dose-dependent weakness
 - d. Diazepam/clonazepam
 - i. Mechanism of action: Benzodiazepine augments GABA_A chloride influx
 - ii. Adverse events: Sedation, weakness, and ataxia
 - iii. Special considerations: May have risk of withdrawal if abruptly discontinued
 - e. Tizanidine
 - i. Mechanism of action: α_2 -Adrenergic agonist; reduces muscle tone through hyperpolarization of motor neurons with a decrease in excitability
 - ii. Adverse events: Sedation, hypotension, asthenia, dry mouth, dizziness, hallucinations, and hepatotoxicity
 - iii. Special considerations: When given with food, absorption increases.
 - f. Botulinum toxin A
 - i. Mechanism of action: Acts as a denervation agent at the nerve terminal end plate by blocking acetylcholine release at the neuromuscular junction. Causes muscle paralysis
 - ii. Given every 3 months as an intramuscular injection at the location of muscle involvement

- iii. Adverse events: Pain at the injection site, excessive weakness, unsteadiness, falls, and fatigue
- iv. Special considerations:
 - (a) AbobotulinumtoxinA is approved in pediatric patients 2 years and older for upper and lower limb spasticity.
 - (b) OnabotulinumtoxinA is approved in pediatric patients 2 years and older for upper and lower limb spasticity. The practice parameter recommends it for localized or segmental spasticity.
 - (c) IncobotulinumtoxinA is approved in adults for upper limb spasticity, including cerebral palsy, and in pediatric patients for upper limb spasticity, excluding spasticity caused by cerebral palsy.
- v. Potential for systemic toxicity from the spread of botulinum toxicity from the injection site (black box warning)
- g. Treatment guidelines

Table 5. Treatment Guideline for Spasticity in Children and Adolescents

Level of Evidence	Localized or Segmental	Generalized
Strong	Botulinum toxin A	
Good		Diazepam
Weak	Tizanidine	
Insufficient	Botulinum toxin B Phenol Alcohol	Dantrolene Baclofen Intrathecal baclofen pump

Information from: Delgado MR, Hirtz D, Aisen M, et al. Quality Standards Subcommittee of the American Academy of Neurology, Practice Committee of the Child Neurology Society. Practice parameter: pharmacologic treatment of spasticity in children with cerebral palsy (an evidence-based review). *Neurology* 2010;74:336-43.

- 2. Dystonia
 - a. Intrathecal baclofen may be effective for dystonia.
 - b. Evidence is insufficient to recommend use of other pharmacologic treatments.
- 3. Drooling
 - a. Nonpharmacologic treatment should be tried first (e.g., good oral hygiene, attention to posture, training in oral motor skills).
 - b. Anticholinergics:
 - i. Mechanism of action: Block the muscarinic receptors in the salivary glands
 - ii. Adverse events include dry mouth, urinary retention, and constipation.
 - iii. Glycopyrrolate is available as a solution (FDA approved in children for sialorrhea).
 - iv. Scopolamine is available as a transdermal patch.
 - v. Benztropine and trihexyphenidyl are available as tablets. Trihexyphenidyl is also available as an elixir.
 - vi. Atropine is available both as an injectable and eye drops that can be used sublingually.
 - c. Botulinum toxin A: Injected into the parotid and submandibular glands. Adverse events include pain, hematoma, swelling of the gland, and infection. Temporary swelling may cause swallowing difficulties.
- 4. Low bone mineral density
 - a. Vitamin D and calcium supplementation may be used if concentrations place the patient at increased risk.
 - b. Bisphosphonates may be considered if the patient has a history of fractures.

5. Sleep
 - a. Nonpharmacologic treatment (e.g., sleep hygiene, parental education) and spasticity management should be tried first.
 - b. Melatonin and gabapentin: Insufficient evidence to recommend for sleep in this population
6. Pain management
 - a. Treat acute pain associated with surgery and other procedures.
 - b. Look for cause of pain and treat accordingly. Consider potential mental health problems such as depression.
 - c. Gabapentin is sometimes used for chronic pain, anxiety, and sleep, but evidence is insufficient in this population.

Patient Case

Questions 10–12 pertain to the following case.

J.N. is a 10-year-old girl (weight 28 kg) with cerebral palsy. Her symptoms of spasticity (muscle stiffness/tightness) are getting worse and are interfering with daily function. The physician prescribes tizanidine 2 mg at bedtime.

10. On which adverse event would J.N. and her family best receive counseling?
 - A. Hypertension.
 - B. Sedation.
 - C. Renal dysfunction.
 - D. Mania.
11. After several months, J.N. returns to the physician's office with worsening symptoms. The physician changes the prescription to oral baclofen. Although this medication is well tolerated by J.N., the muscle tightness continues in her arms, interfering with writing and other activities. The physician initiates onabotulinumtoxinA to be given every 3 months. Although rare, which potentially serious adverse effect would be best to notify J.N. and her family about?
 - A. Hepatic failure.
 - B. Renal failure.
 - C. Systemic toxicity.
 - D. Tardive dyskinesia.
12. After about 1 year of treatment, J.N.'s family continues to report that the medications tried have not helped J.N.'s spasticity symptoms. The physician initiates intrathecal baclofen. After 2 months of improved symptom control, J.N. suddenly becomes confused and irritated, with an elevated temperature. J.N. also is having terrible muscle rigidity, and her spasticity symptoms are worse. Which is the most likely cause of these symptoms?
 - A. Injection-site infection.
 - B. Baclofen toxicity.
 - C. Abrupt discontinuation.
 - D. Inadequate dose.

IV. AUTISM SPECTRUM DISORDERS

A. Epidemiology

1. Prevalence of autism spectrum disorders (ASDs): 1 in 44 children are diagnosed with in the United States.
2. Asperger disorder is one-fifth as common as typical autism, though this disorder is no longer specified in the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*.
3. Autism is 4 times more common in males than in females.
4. Females with autism tend to have greater intellectual disability.

B. Signs and Symptoms

1. *DSM-5* criteria for ASDs changed from *DSM-IV-TR* criteria. *DSM-5* ASDs now include autistic disorder, Asperger disorder, childhood disintegrated disorder, Rett disorder, and pervasive developmental disorder not otherwise specified.
2. Diagnostic domains were reduced from three to two.
 - a. Deficits in social communication and interactions
 - b. Restricted repetitive patterns of behaviors and interests
3. Associated behavioral difficulties
 - a. Hyperactivity
 - b. Obsessive-compulsive phenomena
 - c. Self-injury
 - d. Aggression
 - e. Stereotypies (repetitive or ritualistic movements, posturing, or utterances)
 - f. Tics
 - g. Affective symptoms (depression, mania, mood lability, anxiety)
4. Attention difficulties are common in ASD, and *DSM-5* allows for ADHD as an additional diagnosis.
5. 50% of patients may have severe or profound intellectual disability.

C. Treatment

1. Nonpharmacologic and psychosocial interventions are primary treatment. Consider age and target symptoms when determining specific interventions.
 - a. Behavior therapy
 - b. Speech/language therapy
 - c. Occupational therapy
 - d. Physical therapy
 - e. Social skills and other educational services
 - f. Structural education for parents/caregivers
2. Pharmacotherapy should be recommended for a specific target symptom or comorbid condition. Consider adverse events and avoid polypharmacy.
 - a. Second-generation or atypical antipsychotics:
 - i. Risperidone and aripiprazole are FDA label approved for the treatment of irritability, consisting primarily of physical aggression and severe tantrum behavior associated with autism.
 - ii. One small study has been published investigating olanzapine. Improved group interactions were noted, but global improvement was not significant. Weight gain occurred significantly more often in the olanzapine group. Olanzapine is not FDA label approved.
 - iii. One placebo-controlled study of 149 outpatients 6–17 years of age has been published investigating lurasidone. Results were not statistically significant. Vomiting was reported at a higher rate than in other lurasidone studies, especially in children 6–12 years of age.

- iv. Open-label studies and case series have been reported for quetiapine, ziprasidone, and paliperidone.
- v. Ziprasidone and olanzapine are available in a short-acting intramuscular formulation for acute agitation. Lorazepam intramuscularly administered simultaneously with olanzapine intramuscularly increases the risk of respiratory depression.
- vi. Two retrospective studies and one case series investigating clozapine noted a decrease in aggression and treatment-resistant irritability.
- vii. No studies of long-acting injectable antipsychotics in adolescents with ASD have been published. One observational study of adolescents with other mental illness diagnoses noted tolerability.
- b. First-generation or typical antipsychotics: Haloperidol was used until second-generation antipsychotics were developed.
 - i. Although adverse events limit use, haloperidol, droperidol, and chlorpromazine continue to be used for treatment-resistant irritability and aggression.
 - ii. Haloperidol, droperidol, and chlorpromazine are available in a short-acting intramuscular formulation for acute agitation.

Table 6. Antipsychotics for Target Symptoms of Autism

Drug Name	Age Approved	Target Symptom	Adverse Events	Formulations Available
Aripiprazole	6–17 yr	Irritability Hyperactivity Stereotypies	Fatigue Restlessness Somnolence Vomiting Weight gain	Tablet ODT Oral solution LAI
Chlorpromazine	Not FDA approved in autism	Acute agitation/aggression	Anticholinergic effects EPS Hypotension Somnolence	Tablet Oral solution Short-acting IM
Clozapine	Not FDA approved for autism	Treatment refractory	Anticholinergic effects Agranulocytosis Drooling Hyperglycemia Hyperlipidemia Myocarditis Seizures Somnolence Weight gain	Tablet ODT Oral suspension
Haloperidol	Not FDA approved for autism	Social isolation Stereotypies Hyperactivity Anger-related behaviors	EPS Restlessness Somnolence	Tablet Oral solution Short-acting IM LAIA
Olanzapine	Not FDA approved for autism	Irritability Agitation Stereotypies Hyperactivity	EPS Hyperglycemia Hyperlipidemia Increased liver function test Somnolence Weight gain	Tablet ODT Short-acting IM

Table 6. Antipsychotics for Target Symptoms of Autism (*continued*)

Drug Name	Age Approved	Target Symptom	Adverse Events	Formulations Available
Paliperidone	Not FDA approved for autism	Irritability	EPS Hyperprolactinemia ^a Restlessness Somnolence Weight gain	Tablet LAIA
Quetiapine	Not FDA approved for autism	Irritability	Anticholinergic effects Hyperglycemia Hyperlipidemia Somnolence Weight gain	Tablet
Risperidone	5–16 yr	Severe aggression Temper tantrums Self-injury Hyperactivity Stereotypies Irritability Repetitive behaviors	EPS Hyperprolactinemia ^a Restlessness Somnolence Weight gain	Tablet ODT Oral solution LAIA
Ziprasidone	Not FDA approved for autism	Irritability	EPS QTc prolongation Somnolence	Capsule Short-acting IM

^aHyperprolactinemia can lead to amenorrhea, sexual adverse effects, galactorrhea, gynecomastia, and increased risk of osteoporosis.

EPS = extrapyramidal symptoms; IM = intramuscular(ly); LAI = long-acting injectable; LAIA = long-acting injectable antipsychotic; ODT = orally disintegrating tablet.

- c. Anticonvulsants: Valproic acid, lamotrigine, and levetiracetam have inconsistent results with target symptoms of irritability and repetitive behaviors. Often used for comorbid seizure disorders
- d. Memantine, amantadine, omega-3, L-carnitine, and acetylcysteine: All have been studied with small randomized controlled trials (RCTs), but evidence is insufficient for efficacy. Overall, these agents are well tolerated. None is FDA approved for ASD.
- e. Melatonin: The Sleep Committee of the Autism Treatment Network (ATN) recommends thorough assessment and behavioral interventions before pharmacologic treatment. In ASD, N-acetylserotonin, O-methyltransferase (ASMT) levels are reduced, the final enzymatic reaction in forming endogenous melatonin. Several small RCTs showed efficacy with relatively few adverse events.
- f. Other medications often used in children with ASDs caused by comorbid conditions:
 - i. Selective serotonin reuptake inhibitors (SSRIs) for depression/anxiety
 - ii. α_2 -Agonists, stimulants, and/or atomoxetine for ADHD symptoms
 - iii. Mood stabilizers (valproic acid, lithium) for mania/hypomania
 - iv. Short-acting benzodiazepines for acute anxiety, sleep, or agitation; no evidence to support use

Patient Cases

Questions 13 and 14 pertain to the following case.

E.A. is a 9-year old boy with ASD who presents with symptoms of hyperactivity, stereotypies, and self-injurious behavior.

13. A physician prescribes risperidone for E.A. For which potential adverse effect would E.A. and his family best receive counseling on risperidone use?
 - A. Weight loss and/or anorexia.
 - B. Anticholinergic symptoms like constipation, dry mouth, and blurred vision.
 - C. Male breast tenderness.
 - D. Antipsychotic withdrawal symptoms like seizures.
14. After several years of improved behavior, E.A. begins to have worsening irritability and aggression. The physician would like to change E.A.'s therapy. Which alternative medication would be best?
 - A. Aripiprazole.
 - B. Lurasidone.
 - C. Asenapine.
 - D. Iloperidone.
15. J.P. is a 12-year-old girl (weight 35 kg) with an ASD. For the past few months, she has become more irritable and aggressive and is having emotional outbursts. Her parents are frustrated and looking for help. The physician wants to prescribe an antipsychotic. Given J.P.'s diagnosis and symptoms, which would be best?
 - A. Olanzapine.
 - B. Risperidone.
 - C. Quetiapine.
 - D. Ziprasidone.

V. PEDIATRIC BIPOLAR DISORDER

- A. Epidemiology
 1. Lifetime prevalence of type I bipolar disorder in the general population: 0.4%–1.6%
 2. Lifetime prevalence of type II bipolar disorder in the general population: 0.5%
 3. Pediatric bipolar disorder: Estimated at 1.8%
- B. Definitions
 1. Mania: Mood that is abnormally and persistently elevated, expansive, or irritable and the presence of abnormally increased goal-directed activity or energy that is persistent, lasting most of the day almost every day for at least 1 week. Three or more of the following symptoms (four or more if the mood is simply irritable) are present:
 - a. Inflated self-esteem or grandiosity
 - b. Decreased need for sleep
 - c. Hypervocal or pressured speech
 - d. Flight of ideas or racing thoughts
 - e. Distractibility or continuously changing plans or activities
 - f. Increase in goal-directed activity or psychomotor agitation/physical restlessness

- g. Excessive involvement in risky activities that may have negative consequences (e.g., spending sprees, sexually inappropriate behavior, or risky business ventures). Symptoms must be severe enough to cause functional impairment or hospitalization.
 2. Hypomania: Symptoms are similar to those of mania, but they are persistent, lasting most of the day almost every day for at least 4 days. Three or more symptoms (four or more if the mood is simply irritable) are present. Risky activities are usually not so severe that they require hospitalization.
 3. Major depressive episode: See Pediatric Depression section for symptoms. Children with bipolar depression present with anger and depressed mood and are more likely to have comorbid conduct, anxiety, and substance abuse than those with major depressive disorder.
 4. Type I bipolar disorder: Criteria for one manic episode must be met. One lifetime manic episode must occur to have this diagnosis. A major depressive episode may or may not always occur.
 5. Type II bipolar disorder: Criteria for one hypomanic episode and one major depressive episode must be met with no history of a manic episode.
 6. Cyclothymic disorder: For children and adolescents: At least 1 year of several periods of hypomanic symptoms in those who have never met the criteria for manic episodes and in those with several periods of depressive symptoms who have never met the criteria for a major depressive episode
- C. Treatment
1. American Academy of Child and Adolescent Psychiatry Practice Parameter defined in 2007 for treatment of children and adolescents
 - a. Recommends using pharmacotherapy for mania
 - b. Ongoing to prevent relapse and possibly lifelong
 - c. Baseline and follow-up monitoring for symptoms, adverse effects, and laboratory monitoring
 - d. ECT (electroconvulsive therapy) may be used if medications are not tolerated.
 - e. Antidepressants may be used for bipolar depression in combination with a mood stabilizer.
 2. Treatment guidelines
 - a. 2007 Practice Parameter refers to 2005 guideline in Table 7

Table 7. Treatment Guideline Developed in 2005 for Children and Adolescents

Stage	Manic or Mixed without Psychosis	Manic or Mixed with Psychosis
1	Second-generation antipsychotic (olanzapine, quetiapine, risperidone) or mood stabilizer (lithium, valproic acid, carbamazepine) If partial response, may combine two (not two antipsychotics)	Mood stabilizer (lithium, valproic acid, carbamazepine) plus second-generation antipsychotic
2	Switch to another agent if monotherapy not already tried. If partial response, augment with second agent	Mood stabilizer (lithium, valproic acid, carbamazepine) + second-generation antipsychotic (combination not tried in stage 1) Partial response: Use lithium and valproic acid or carbamazepine and a second-generation antipsychotic

Table 7. Treatment Guideline Developed in 2005 for Children and Adolescents (*continued*)

Stage	Manic or Mixed without Psychosis	Manic or Mixed with Psychosis
3	Monotherapy agent not tried in stage 1 or 2	Alternative mood stabilizer or second-generation antipsychotic added to two-medication combination
4	Combination of two agents. If partial response, may add third agent	Combination of two mood stabilizers and second-generation antipsychotic
5	Monotherapy with oxcarbazepine, ziprasidone, or aripiprazole	Monotherapy with oxcarbazepine, ziprasidone, or aripiprazole
6	ECT (adolescents) or clozapine	ECT (adolescents) or clozapine

ECT = electroconvulsive therapy.

Information from: Kowatch RA, Fristad M, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2005;44:213-35.

- b. Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline includes bipolar depression recommendations.
- c. National Institute for Health and Care Excellence (NICE) guidelines updated in 2020 recommend against valproic acid in females of childbearing potential.
- d. Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents updated to include FDA label-approved agents

Table 8. Other Guidelines for Bipolar Disorder in Children and Adolescents

	Canadian Network for Mood and Anxiety Treatments (2018)	National Institute for Health and Care Excellence (2014, updated 2020)	Florida Best Practice Psychotherapeutic Medication Guidelines (2019)
First line Level 1	<u>Mania</u> : Lithium, risperidone, aripiprazole, asenapine, or quetiapine <u>Depression</u> : Lurasidone	Mania: Aripiprazole Depression: CBT	<u>Mania/mixed</u> (10–17 yr of age): Aripiprazole, risperidone, quetiapine, or asenapine <u>Classic mania</u> (12–17 yr of age): Lithium <u>Depression</u> (10–17 yr of age): Lurasidone
Second line Level 2	<u>Mania</u> : Olanzapine, ziprasidone, lithium + quetiapine <u>Depression</u> : Lithium or lamotrigine	<u>Mania</u> : Consider other antipsychotics or lithium <u>Depression</u> : Consider olanzapine/fluoxetine, quetiapine, olanzapine, lamotrigine, or lithium	<u>Mania/mixed</u> : Monotherapy with antipsychotic not tried in level 1 or olanzapine or lithium (12–17 yr of age) <u>Depression</u> : Olanzapine/fluoxetine

Table 8. Other Guidelines for Bipolar Disorder in Children and Adolescents (*continued*)

	Canadian Network for Mood and Anxiety Treatments (2018)	National Institute for Health and Care Excellence (2014, updated 2020)	Florida Best Practice Psychotherapeutic Medication Guidelines (2019)
Third line Level 3	<u>Mania: Valproate</u> <u>Depression:</u> Olanzapine/fluoxetine + quetiapine		<u>Mania/mixed:</u> Reassess diagnosis; monotherapy with antipsychotic not tried in level 1 or 2, or combination antipsychotic with lithium or valproate <u>Depression:</u> Consider lamotrigine
Level 4			Consider clozapine or ECT
Not recommended	Oxcarbazepine	Valproate in females of childbearing potential Gabapentin	Two antipsychotics concurrently unless cross-tapering

CBT = cognitive behavior therapy; ECT = electroconvulsive therapy.

Information from: Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANM/AT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord* 2018;20:97-170; National Institute for Health and Care Excellence (NICE). Clinical Guideline CG185. Bipolar Disorder: Assessment and Management. Available at www.nice.org.uk/guidance/cg185; University of South Florida, Florida Medicaid Drug Therapy Management Program sponsored by the Florida Agency for Health Care Administration (AHCA). 2018-2019 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents. 2019. Available at 2018-19-FL-Best-Practice-Medication-Child-Adolescent_Online1.pdf (floridabhcenter.org).

3. Lithium

- a. Indicated for acute mania, mixed episode, or maintenance for children 7 years and older. Off-label indication for depression
- b. Mechanism of action: Unknown; normalizes or inhibits second messenger systems; decreases serotonin reuptake and increases postsynaptic serotonin receptor sensitivity; enhances GABA activity; reduces glutamate activity; modulates calcium metabolism
- c. Pharmacokinetics: Linear, not metabolized, half-life 24 hours, renal elimination
- d. Dose
 - i. Immediate release: For children 7 years and older
 - (a) Consider phase (acute vs. maintenance) and weight; titrate to therapeutic concentration.
 - (b) For renal impairment, start low and titrate slowly; monitor frequently.
 - ii. Extended release: Children 12 years and older
 - (a) Consider weight; give in two divided doses.
 - (b) Renal impairment: For creatinine clearance 10–50 mL/minute/1.73 m², administer 50%–75% of normal dose. For creatinine clearance less than 10 mL/minute/1.73 m², administer 25%–50% of normal dose.
 - iii. Dosage forms
 - (a) Lithium carbonate available in 150-, 300-, and 600-mg capsules; 300-mg tablets
 - (b) Lithium carbonate extended release available in 300- and 450-mg tablets
 - (c) Lithium citrate oral solution 8 mEq/5 mL: Each 5 mL contains 8 mEq of lithium ion; the equivalent of 300 mg of lithium carbonate

- e. Therapeutic concentrations: 0.8–1.2 mEq/L for acute treatment. Maintenance treatment: 0.6–1.0 mEq/L. Obtain concentrations 4–5 days after initiation.
- f. Adverse effects:
 - i. Nausea, vomiting, diarrhea, hand tremor, impaired cognition, and drowsiness
 - ii. Mild toxicity: Nausea/vomiting, loose stools, lethargy, drowsiness, coarse hand tremor, muscular weakness
 - iii. Moderate toxicity: Severe nausea, vomiting, diarrhea, confusion, dysarthria, nystagmus, ataxia, myoclonic twitches, electrocardiographic (ECG) changes
 - iv. Severe toxicity: Severe nausea, vomiting, diarrhea, impaired consciousness, increased deep tendon reflexes, seizures, syncope, coma, ECG changes, renal insufficiency, kidney failure
- g. Drug interactions: Medications that affect the kidney
 - i. Increase lithium concentrations and potential toxicity
 - (a) Nonsteroidal anti-inflammatory drugs
 - (b) Diuretics (thiazide and loop diuretics)
 - (c) Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers
 - ii. Decrease lithium concentrations and decrease efficacy
 - (a) Caffeine
 - (b) Theophylline
- 4. Valproic acid: See Seizure Disorders section for mechanism of action, adverse events, and doses. Approved in adults for mania and mixed episodes. Not FDA label approved in children and adolescents for mania
- 5. Carbamazepine: See Seizure Disorders section for mechanism of action, adverse events, and doses. Approved for adults for manic or mixed episodes. Not FDA label approved for children and adolescents
- 6. Lamotrigine: See Seizure Disorders section for mechanism of action, adverse events, and doses. Approved in adults for long-term maintenance treatment. Not helpful for mania. Not FDA label approved in children and adolescents for bipolar disorder
- 7. Second-generation antipsychotics
 - a. Mechanism of action: Dopamine-2 and serotonin-2A receptor blockers postsynaptically
 - b. Olanzapine
 - i. FDA label approved in those 13–17 years of age for manic and mixed episodes
 - ii. Dose:
 - (a) Children 4–5 years: Initial 1.25 mg daily. Increase dose weekly. Max 10 mg/day
 - (b) Children 6–18 years: Initial 2.5 mg daily. Titrate to target 10 mg/day. Max 20 mg/day
 - iii. Adverse effects: Sedation, weight gain, hyperlipidemia, hyperglycemia, increased liver function test, extrapyramidal symptoms
 - c. Olanzapine/fluoxetine
 - i. FDA label approved in those 10–17 years of age for depressive episodes associated with bipolar disorder
 - ii. Dose:
 - (a) Initial 3/25 mg once daily at bedtime. Max dose: 12/50 mg daily at bedtime
 - (b) Discontinue gradually.
 - iii. Adverse effects: Similar to olanzapine and fluoxetine
 - d. Quetiapine
 - i. FDA label approved in those 10–17 years of age for manic episodes
 - ii. Dose: Start with 25 mg twice daily. Increase to 200 mg twice daily by day 5. Max dose 300 mg twice daily. Extended-release formulation is dosed once daily.
 - iii. Adverse effects: Sedation, weight gain, anticholinergic effects, orthostatic hypotension

- e. Risperidone
 - i. FDA label approved in those 10–17 years of age for manic and mixed episodes
 - ii. Dose: Initial 0.5 mg once daily. Increase by 0.5–1 mg/day. Max dose 6 mg/day. However, doses greater than 2.5 mg/day have no extra benefit in this age group.
 - iii. Adverse effects: Sedation, extrapyramidal effects, hyperprolactinemia, weight gain, orthostatic hypotension
- f. Aripiprazole
 - i. FDA label approved for those 10–17 years of age for manic and mixed episodes
 - ii. Dose: Initial 2 mg daily for 2 days; then 5 mg daily for 2 days. Increase to 10 mg daily by day 5. Max dose 30 mg/day
 - iii. Adverse effects: Restlessness, drooling, drowsiness, extrapyramidal symptoms, fatigue, hypersomnia, lethargy, sedation, weight gain, nausea
- g. Asenapine
 - i. FDA label approved for those 10–17 years of age for manic and mixed episodes
 - ii. Dose: Initial 2.5 mg sublingually twice daily. After 3 days, may increase to 5 mg twice daily. Max dose: 10 mg sublingually twice daily
 - iii. Black cherry–flavored sublingual tablets are preferred by patients.
 - iv. Instruct patients not to swallow tablet. Place under tongue and let dissolve completely. Eating and drinking should be avoided for 10 minutes.
 - v. Adverse effects: Somnolence, dizziness, nausea, increased appetite, weight gain, fatigue, distortion of sense of taste, oral paresthesia. Pediatric patients appear to be more sensitive to dystonia with initial dosing if escalation schedule is not followed.
- h. Lurasidone
 - i. FDA label approved for those 10–17 years of age for bipolar depression monotherapy
 - ii. Dose: Initial 20 mg daily. Range: 20–80 mg daily
 - iii. Adverse effects: Nausea, weight increase, and insomnia
 - iv. Take with food to increase absorption.
- i. Other antipsychotics are approved in adults (ziprasidone).
- j. Clozapine is FDA label approved for suicidal behavior in adult patients with schizophrenia or schizoaffective disorder.

Patient Cases

Questions 16–18 pertain to the following case.

M.W. is a 16-year-old female adolescent who presents to the ED with flight of ideas, rapid speech, irritability, and hyperactivity. She is wearing a silver top with sequins and heavily applied makeup. She flirts with the young male resident covering the ED. Her parents are concerned about her behavior, especially with her overt sexual conduct. This seems to be a new development in the past few weeks, and it has caused marked impairment in her functioning at school. No psychotic symptoms are present. Laboratory tests show no abnormalities, and her toxicology screen is negative. She denies using drugs or alcohol. After a thorough workup, M.W. is given a diagnosis of type I bipolar disorder, current episode mania.

16. According to the treatment guidelines, which is the most appropriate first-stage recommendation?
- A. Lithium.
 - B. Lithium plus olanzapine.
 - C. Olanzapine plus risperidone.
 - D. Valproic acid plus quetiapine.

Patient Cases (*continued*)

17. The physician prescribes lithium for M.W. After a few days, her lithium dose is 600 mg twice daily. A lithium concentration is ordered after 5 days at this dose. Which most accurately represents the target range for this therapeutic concentration?
- A. 0.2–0.5 mEq/L.
 - B. 0.6–0.8 mEq/L.
 - C. 0.8–1.2 mEq/L.
 - D. 1.3–1.5 mEq/L.
18. After M.W. is stabilized on lithium, she is discharged home with instructions to follow up in 1 month and repeat another lithium concentration. Two weeks later, during her menstrual cycle, she starts over-the-counter ibuprofen and presents to the ED. Which pair of symptoms would she most likely present with?
- A. Ataxia and a coarse tremor.
 - B. Liver failure and jaundice.
 - C. Pancreatitis and abdominal pain.
 - D. Hyperactivity and hallucinations.
19. L.T. is a 15-year-old female adolescent with a diagnosis of bipolar disorder, current episode of acute depression. She presents to the ED after overdosing on 10 lorazepam tablets. After being medically cleared, she is admitted to the pediatric behavioral health care unit. Which medication may be most appropriate for L.T. at this time?
- A. Valproic acid.
 - B. Lamotrigine.
 - C. Oxcarbazepine.
 - D. Carbamazepine.

VI. ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

- A. Epidemiology
 - 1. Estimated at 6%–9% in school-aged children
 - 2. More commonly diagnosed in boys than in girls by 4:1
- B. Symptoms
 - 1. Inattention: Six or more (five or more for 17 years or older) that affect function
 - a. Does not pay attention to details or makes careless mistakes in schoolwork
 - b. Difficulty sustaining attention in tasks or play activity
 - c. Does not seem to listen when spoken to directly
 - d. Does not follow through on instructions or does not finish schoolwork, chores, or work duties
 - e. Difficulty organizing tasks and activities
 - f. Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
 - g. Loses items necessary for tasks or activities
 - h. Easily distracted by external stimuli
 - i. Forgetful in daily activities

2. Hyperactivity and impulsivity: Six or more (five or more for 17 years or older) that affect function
 - a. Fidgets with or taps hands or feet or squirms in seat
 - b. Leaves seat in situations when remaining seated is required
 - c. Runs about or climbs when it is unacceptable
 - d. Difficulty playing or engaging in leisure activities quietly
 - e. Is often “on the go” acting as if “driven by a motor”
 - f. Talks excessively
 - g. Blurts out answers before questions have been completed
 - h. Has difficulty waiting his or her turn
 - i. Interrupts or intrudes on others
3. Symptoms must be present before the patient is 12 years of age and must occur in two settings.

C. Treatment

1. Treatment guidelines

Table 9. Guidelines for Attention-Deficit/Hyperactivity Disorder

Level of Intervention	American Academy of Child and Adolescent Psychiatry (2007)	American Academy of Pediatrics (2019)	Florida Best Practice Psychotherapeutic Medication Guideline (2019)
I	Methylphenidate, amphetamine	4–5 yr of age: Behavior therapy alone 6–18 yr of age: Methylphenidate or amphetamine; option to choose level II medication on the basis of patient-specific factors	< 6 yr of age: Behavior therapy alone 6–17 yr of age: Methylphenidate or amphetamine IR or XR monotherapy; or α_2 -agonist monotherapy
II	Atomoxetine	4–5 yr of age: Methylphenidate Age 6–18: Atomoxetine guanfacine XR or clonidine XR	< 6 yr of age: Methylphenidate IR monotherapy 6–17 yr of age: Stimulant and α_2 -agonist XR combination; or atomoxetine monotherapy
III	If none of the above is satisfactory, review diagnosis; consider behavior therapy		< 6 yr of age: Atomoxetine 6–17 yr of age: α_2 -Agonist IR monotherapy or combination with stimulant
IV	Bupropion, TCA, or α_2 -agonist		< 6 yr of age: Amphetamine (3- to 5-yr approved formulations only) or α_2 -agonist 6–17 yr of age: Reconsider diagnosis; consider bupropion or TCA

IR = immediate release; TCA = tricyclic antidepressant; XR = extended release.

Information from: American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescent with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2007;46:894-921; American Academy of Pediatrics (AAP). ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention deficit/hyperactivity disorder in children and adolescents. *Pediatrics* 2019;144:e20192528; University of South Florida, Florida Medicaid Drug Therapy Management Program sponsored by the Florida Agency for Health Care Administration (AHCA). 2018-2019 Florida Best Practice Psychotherapeutic Medication Guidelines for Children and Adolescents. 2019. Available at 2018-19-FL-Best-Practice-Medication-Child-Adolescent_Online1.pdf (floridabhcenter.org).

2. Nonpharmacologic treatment
 - a. BPT (behavioral parent training)
 - b. Behavioral interventions
 - c. School-focused interventions
 - d. Child-focused interventions
 - e. CBT
3. Pharmacologic treatment
 - a. Methylphenidate and dexamethylphenidate stimulants – Mechanism of action: Dopamine and norepinephrine transport blockers resulting in sympathomimetic activity in the CNS
 - b. Amphetamine stimulants (amphetamine, dextroamphetamine, mix salts, lisdexamfetamine) – Mechanism of action: Dopamine and norepinephrine transport blocker; stimulates the release of dopamine and norepinephrine into the presynaptic nerve cell
 - c. Adverse effects of stimulants
 - i. Increase in blood pressure/heart rate
 - ii. Psychosis or manic symptoms
 - iii. Decreased appetite
 - (a) Eat high-calorie breakfast and dinner/bedtime.
 - (b) Assess for weight loss.
 - iv. Insomnia (give in morning or reduce afternoon dose)
 - v. GI distress (take with high-fat meal)
 - vi. Irritability (rebound phenomena vs. potential suicide ideation sign)
 - vii. Headache
 - viii. Tics (prior history)
 - ix. Seizures: Treat underlying seizure disorder first with adequate dose to prevent breakthrough seizures.
 - x. Growth suppression
 - (a) Drug holidays: Discontinue use during the summer or on weekends.
 - (b) Consider risk-benefit.
 - (c) Over time, patients seem to catch up, except children with small stature.
 - d. Choice of stimulant depends on formulation, onset of action, time to peak, and insurance coverage.
 - i. lisdexamfetamine: prodrug of dextroamphetamine designed to prevent abuse
 - ii. Patch formulation may be removed early for duration flexibility.
 - e. Selective norepinephrine reuptake inhibitor – Atomoxetine, viloxazine
 - i. Adverse effects: GI discomfort, nausea, loss of appetite, headache, insomnia, irritability, fatigue, dizziness, severe liver function (rare), increased blood pressure (rare), suicidal thinking, or change in behavior (black box warning)
 - ii. Hepatically metabolized via CYP2D6 and CYP2C19
 - f. α_2 -Adrenergic agonists
 - i. Mechanism of action: Central α_2 -adrenergic receptor agonists inhibit presynaptic norepinephrine release and postsynaptically increase blood flow to the prefrontal cortex.
 - ii. Extended-release guanfacine and clonidine are FDA label approved. Immediate-release formulations are NOT FDA label approved for ADHD.
 - iii. Controlled data are limited for the immediate-release formulations.
 - iv. Adverse effects: Bradycardia, hypotension
 - g. Bupropion – Mechanism of action: Reuptake inhibitor of dopamine and norepinephrine
 - i. Adverse events: Dry mouth, dizziness, tachycardia, anorexia, akinesia, auditory disturbance, anxiety, insomnia
 - ii. Warnings/precautions: Suicidal ideation (black box warning), seizures, caution with cardiac disease, activation of mania/hypomania

- iii. Max dose varies with formulation
- iv. Contraindicated in patients with seizures, anorexia nervosa, or bulimia nervosa
- h. Tricyclic antidepressants (TCAs) have historically been used, but because of their potential adverse effects, they are not preferred.

Patient Cases

20. W.B. is a 5-year-old boy (weight 25 kg) with a diagnosis of ADHD. According to the most recent guidelines published in 2019, which most accurately depicts first-line therapy?

- A. Behavior therapy alone.
- B. Atomoxetine.
- C. Guanfacine XR.
- D. Methylphenidate.

Questions 21 and 22 pertain to the following case.

R.K. is a 13-year-old female adolescent (weight 45 kg) with a diagnosis of ADHD.

21. According to the most recent guidelines published in 2019, which is best for first-line therapy?

- A. Clonidine XR.
- B. Atomoxetine.
- C. Guanfacine XR.
- D. Methylphenidate.

22. The physician believes R.K. may have some substance abuse potential and wants to prescribe an amphetamine-based product that is a prodrug. Which best reflects the product that is available as a prodrug?

- A. Amphetamine/dextroamphetamine.
- B. Dextroamphetamine.
- C. Lisdexamfetamine.
- D. Amphetamine/dextroamphetamine XR.

VII. PEDIATRIC DEPRESSION**A. Epidemiology**

1. About 11% of adolescents have a depressive disorder by age 18.
2. Estimated prevalence is 2% in children and 4%–8% in adolescents.
3. Male-to-female ratio of 1:1 during childhood and 1:2 during adolescence
4. The risk of depression increases as a child gets older; increases 2- to 4-fold after puberty, especially in females
5. According to the World Health Organization, major depression is the leading cause of disability among Americans 15–44 years of age.
6. In 2020, suicide was the third leading cause of death for youth 15–24 years of age. For youth 10–14 years of age, suicide was the second leading cause of death.
7. Suicide attempts of adolescents who identify as lesbian, gay, or bisexual are 4 times higher than of adolescents who identify as heterosexual.

8. Suicide attempts and self-harm behavior are more common in girls than in boys.
9. Non-Hispanic American Indian/Alaska Native youth are most at risk, with suicide rates of 33:100,000 and suicide attempt rates of 25.5%.
10. 40%–90% of pediatric patients have comorbidities.

B. Signs and Symptoms

1. The *DSM-5* criteria for major depressive disorder include five or more of the following symptoms, and the patient must have either depressed mood or loss of interest or pleasure. Symptoms must occur almost every day for at least 2 weeks and result in a change in function.
 - a. Depressed mood
 - b. Lack of interest or pleasure in daily activities
 - c. Significant changes in weight (increase or decrease)
 - d. Significant changes in sleep (insomnia or hypersomnia)
 - e. Psychomotor agitation or retardation
 - f. Fatigue or decreased energy
 - g. Feelings of worthlessness or inappropriate guilt
 - h. Decreased concentration or difficulty making decisions
 - i. Recurrent thoughts of death, suicidal ideation, or suicidal attempt
2. Signs and symptoms differences in children and adolescents compared with adults:
 - a. Depressed mood may be expressed as more of an irritable mood.
 - b. Mood lability
 - c. Low frustration tolerance
 - d. Temper tantrums
 - e. More physical complaints or feeling sick
 - f. Social withdrawal or refusing to go to school
 - g. May not verbalize feelings of depression
 - h. Tend to have fewer melancholic symptoms, delusions, and suicide attempts than adults

C. Treatment

1. General treatment principles
 - a. Treatment guidelines recommend supportive therapy and psychoeducation for mild depression.
 - b. If, after 6–8 weeks, symptoms persist, antidepressants and/or psychotherapy is indicated.
 - c. If after another 6–8 weeks with no improvement: Combination of antidepressants and psychotherapy should be considered, if not already tried.
 - d. If improvement occurs, treatment should continue for 6–24 months. Monitoring should be done monthly for at least the first year.
 - e. Monitor for the emergence of adverse events during pharmacotherapy treatment.
2. SSRIs
 - a. Mechanism of action: Inhibition of presynaptic serotonin reuptake by inhibition of the serotonin transporter in the neurons of the CNS
 - b. Onset and duration of action: Some symptoms such as agitation or anxiety may improve within days to weeks. After 2–4 weeks of treatment, other targets of systems such as depressed mood should improve, including the return of pleasurable experiences and the subsiding of suicidal thoughts.
 - c. Adverse effects: Anxiety, insomnia, sedation, headache, nausea, diarrhea, anorexia, sexual dysfunction
 - d. Serotonin syndrome:
 - i. Occurs with the use of one or more serotonergic agents, particularly combinations of MAOIs and inhibitors of serotonin reuptake
 - ii. Symptoms include mental status changes, autonomic hyperactivity, and neuromuscular abnormalities and can be life threatening.

- e. Serotonin discontinuation syndrome
 - i. Risk with SSRIs with a shorter half-life (e.g., paroxetine)
 - ii. Occurs when abruptly discontinuing the serotonergic agent
 - iii. Symptoms: Anxiety, irritability, sadness, insomnia, headache, nausea, nightmares or vivid dreams, electric shock sensations; not life threatening
 - iv. Prevent by slowly tapering the serotonergic antidepressant slowly over a few weeks.
- f. Fluoxetine is the only antidepressant that is FDA label approved for the treatment of depression in children younger than 12 years. It is also FDA label approved for the treatment of obsessive-compulsive disorder.
- g. Fluoxetine and escitalopram are the only two SSRIs with FDA label approval for use in adolescent depression.
- h. RCTs of sertraline and citalopram over placebo have shown positive results. Sertraline is FDA label approved for obsessive-compulsive disorder in those 6–17 years of age.
- i. Paroxetine has been studied, but only one of three studies showed positive results.
- j. Fluvoxamine is approved for obsessive-compulsive disorder in those 8 years and older but not for depression.
- k. Vilazodone has been studied, but both studies showed not effective in those 7–17 years of age.
- l. Vortioxetine has been studied, but the study showed it was not effective in those 12–17 years of age.

Table 10. Selective Serotonin Antidepressant Doses and Pharmacokinetics

Drug Name	Pediatric Indication	Half-Life	Active Metabolite	Oxidative Enzymes
Escitalopram	FDA label approved for ≥ 12 yr	27–32 hr	No	3A4, 2C19
Fluoxetine	FDA label approved for ≥ 8 yr	4–6 days	Yes (half-life is 7–9 days)	2C9, 2D6
Citalopram	Not FDA approved	35 hr	No	3A4, 2C19, 2D6
Fluvoxamine	Not FDA approved for depression	16 hr	No	1A2, 2D6
Paroxetine	Not FDA approved for depression	24 hr	No	2D6
Sertraline	Not FDA approved for depression	26 hr	<i>N</i> -desmethylsertraline (half-life 66–80 hr)	2C9, 2C19, 2D6, 3A4

3. Selective serotonin and norepinephrine inhibitors
 - a. Mechanism of action: Inhibition of presynaptic serotonin and norepinephrine reuptake by inhibition of the serotonin and norepinephrine transporter in the neurons of the CNS
 - b. Safety and efficacy have not been established for depression or anxiety disorders in pediatric patients.
 - c. Studies have shown no difference between treatment and placebo for venlafaxine and duloxetine.
 - d. Adverse events are similar to those of SSRIs.
 - e. Monitor for high blood pressure.
4. Bupropion
 - a. Studied in ADHD but not FDA indicated
 - b. No RCTs for depression in pediatric patients
5. Mirtazapine: One study showed no difference between mirtazapine and placebo.

6. TCAs
 - a. Meta-analysis showed that SSRIs had better efficacy and were better tolerated.
 - b. RCTs have not shown greater efficacy than placebo.
 - c. Risk of overdose and death can occur with TCAs. ECG changes can occur with increased doses.
7. Ketamine and esketamine: One small, open-label study shows decreased symptoms with ketamine. No RCTs of esketamine in children and adolescents.
8. A meta-analysis of 34 trials, 5260 participants, and 14 antidepressants showed that only fluoxetine was more effective than placebo; fluoxetine was more tolerable than duloxetine and imipramine; and imipramine, venlafaxine, and duloxetine were discontinued more often than placebo because of adverse events.
9. Suicide risk in children and adolescents
 - a. All antidepressants have a black box warning for increased suicidal thinking and behavior in children, adolescents, and young adults.
 - b. Meta-analysis of RCTs showed benefits of antidepressants.
 - c. Risk of increased suicidal thinking is about 2%.
 - d. No evidence of increased suicide attempts

Patient Case

Questions 23–25 pertain to the following case.

B.B. is a 10-year-old boy who says that he is sick and does not want to go to school. On further questioning, he is unable to specify his symptoms. He has been irritable, has had temper tantrums, has a low frustration tolerance, and has been drawing pictures of weapons. He has been preoccupied with thoughts of death. He is given a diagnosis of depression.

23. Which antidepressant is best for B.B.?
 - A. Paroxetine.
 - B. Fluoxetine.
 - C. Sertraline.
 - D. Bupropion.
24. Which best depicts the potential adverse effect that is listed as a black box warning and that the parents of B.B. must be counseled on and notified about?
 - A. Pancreatitis.
 - B. Agranulocytosis.
 - C. Diabetes insipidus.
 - D. Suicidal ideation.
25. If, after 4 weeks of treatment, B.B. has not responded to treatment, which most accurately depicts the medication that has evidence in studies of pediatric patients, even though it is not FDA indicated for pediatric depression?
 - A. Venlafaxine.
 - B. Mirtazapine.
 - C. Sertraline.
 - D. Bupropion.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

Ibuprofen is the only choice with clinical trials showing efficacy for acute treatment (Answer A is correct). Efficacy evidence for sumatriptan is available for the nasal spray and subcutaneous formulations but not for the oral formulation. Oral sumatriptan is only approved when combined with naproxen (Answer C is incorrect). Prochlorperazine may be beneficial even without nausea and vomiting present, but ibuprofen has more evidence (Answer B is incorrect). Topiramate is useful for prophylaxis but not for acute treatment (Answer D is incorrect).

2. Answer: D

Of the choices, topiramate is the only agent useful for prophylaxis (Answer D is correct). The other three agents are for acute treatment (Answers A and B are incorrect). Oral sumatriptan lacks sufficient evidence to support its use in adolescents when used alone (Answer C is incorrect).

3. Answer: C

Because the patient is vomiting, a non-oral formulation is recommended (Answer B is incorrect). Sumatriptan nasal spray is the only choice with evidence of efficacy in a non-oral formulation (Answer C is correct). Valproic acid is for prophylaxis (Answer D is incorrect). Opioids should be avoided (Answer A is incorrect).

4. Answer: A

Because the laboratory value is below the therapeutic concentration of 10–40 mcg/mL and the patient still has seizure episodes, the dose should be increased because the patient does not have good seizure control (Answer A is correct). Because the patient continues to have seizures and the therapeutic concentration is low, the dose should not remain the same or be lowered (Answers B and C are incorrect). The dose should be increased to a therapeutic concentration before adding another medication (Answer D is incorrect).

5. Answer: C

Gingival hyperplasia and hirsutism are both common adverse effects of phenytoin (Answers A and B are incorrect). Oxcarbazepine, which is hepatically cleared, does not affect renal function (Answer D is incorrect). Hyponatremia is more common with oxcarbazepine than with carbamazepine (Answer C is correct).

6. Answer: C

The dosage recommendation according to the manufacturer is to initiate lamotrigine with an every-other-day schedule when used concurrently with valproic acid (Answer C is correct). The recommended starting dose daily is for monotherapy (Answer A is incorrect). Twice daily of the recommended starting dose or twice the daily dose are options when lamotrigine is used concurrently with enzyme inducers (Answers B and D are incorrect).

7. Answer: A

Rash is the main concern with the concomitant use of valproic acid (Answer A is correct). The other three types of adverse events are common with valproic acid (Answers B–D are incorrect).

8. Answer: D

Memory and concentration difficulties have been reported with topiramate (Answer D is correct). The other three adverse events are more common with other antiepileptics, including valproic acid, lamotrigine, phenytoin, and carbamazepine (Answers A–C are incorrect).

9. Answer: D

Given the scenario and the rapid increase in the patient's temperature, this is probably a febrile seizure (Answer D is correct). The other diagnoses cannot be determined with just one seizure (Answers A–C are incorrect).

10. Answer: B

One of the most common adverse effects of tizanidine is sedation (Answer B is correct). Tizanidine is more likely to cause hypotension than hypertension (Answer A is incorrect). Renal dysfunction and mania are adverse effects of baclofen (Answers C and D are incorrect).

11. Answer: C

Although rare, the botulinum toxin can become systemic if it spreads from the injection site (Answer C is correct). The botulinum toxin does not cause direct harm to either the liver or the kidney (Answers A and B are incorrect). Tardive dyskinesia is a long-term adverse effect associated with dopamine receptor blockers (Answer D is incorrect).

12. Answer: C

This scenario probably suggests an abrupt discontinuation, and the family should ensure the pump is not empty (Answer C is correct). The symptoms may also reflect an infection, but not the return of spasticity (Answer A is incorrect). Although an inadequate dose may explain the inadequate control of spasticity symptoms, it does not explain the change in the patient's mental status or temperature (Answer D is incorrect). An overdose of baclofen may explain the mental status changes, but not the change in temperature or inadequate control of spasticity symptoms (Answer B is incorrect).

13. Answer: C

Risperidone can increase prolactin because of its dopamine receptor-blocking mechanism (Answer C is correct). Other second-generation antipsychotics may also increase prolactin, but not to the same extent as risperidone. Olanzapine, quetiapine, and ziprasidone have rates of prolactinemia similar to each other, but less than risperidone. Aripiprazole has the lower rate of prolactinemia. Antipsychotics are more likely to cause weight gain than weight loss (Answer A is incorrect). Risperidone has a lower rate of anticholinergic adverse effects than other antipsychotics (Answer B is incorrect). Seizures are not a common withdrawal symptom of antipsychotics (Answer D is incorrect).

14. Answer: A

Aripiprazole is the only other antipsychotic indicated for autism among the choices (Answer A is correct). Lurasidone, iloperidone, and asenapine have not been studied in this population (Answers B–D are incorrect).

15. Answer: B

Of the choices, risperidone is the only antipsychotic indicated for this patient's symptoms (Answer B is correct). Olanzapine has been studied for this indication, but it lacks an FDA indication for these symptoms (Answer A is incorrect). Quetiapine and ziprasidone lack sufficient data for recommendation over risperidone and do not carry the indication for autism disorder (Answers C and D are incorrect).

16. Answer: A

According to the treatment guidelines, monotherapy is recommended for the initial stage when treating mania without psychosis (Answer A is correct). Olanzapine

may be added to lithium if a partial response occurs with lithium monotherapy (Answer B is incorrect). Valproic acid plus quetiapine may be tried after other treatment trials have failed (Answer D is incorrect). Regimens containing two antipsychotics are not recommended (Answer C is incorrect).

17. Answer: C

The recommended therapeutic range for treating mania is 0.8–1.2 mEq/L (Answer C is correct). The therapeutic range of 0.6–0.8 mEq/L is recommended for maintenance therapy (Answer B is incorrect). The range of 0.2–0.5 mEq/L is too low for an effect to occur (Answer A is incorrect). Toxic symptoms start to occur when the concentration rises above 1.2 mEq/L (Answer D is incorrect).

18. Answer: A

Ataxia is a CNS symptom that can occur with moderate toxicity (Answer A is correct). Lithium is not metabolized and is therefore unlikely to cause liver or pancreatic problems (Answers B and C are incorrect). Hyperactivity is a symptom of mania (Answer D is incorrect). Toxic symptoms are more likely to be somnolence, syncope, seizures, and coma.

19. Answer: B

Of these four medications, lamotrigine is recommended for bipolar depression (Answer B is correct). The other three antiepileptics are recommended for mania or mixed episode symptoms (Answers A, C, and D are incorrect).

20. Answer: A

According to the American Academy of Pediatrics (AAP) guidelines published in 2019, the first-line treatment for children 4–5 years of age is behavior therapy (Answer A is correct). Only methylphenidate is considered a second-line medication (Answer D is incorrect). The other agents are not recommended in this age group (Answers B and C are incorrect).

21. Answer: D

According to the AAP guidelines published in 2019, the first-line treatment of 6- to 18-year-olds is methylphenidate or amphetamine products (Answer D is correct). Clonidine XR, guanfacine XR, and atomoxetine are second-line agents (Answers A–C are incorrect).

22. Answer: C

Lisdexamfetamine is a prodrug that converts to amphetamine (Answer C is correct). The other three medications are not prodrugs (Answers A, B, and D are incorrect).

23. Answer: B

Fluoxetine is the only FDA-indicated medication for depression in children younger than 12 (Answer B is correct). Sertraline has been studied in pediatric patients but does not have the FDA indication (Answer C is incorrect). Paroxetine was effective in only one of three studies (Answer A is incorrect). Bupropion has not been studied for depression (Answer D is incorrect). Because no other medications have been prescribed for this patient, it is reasonable to start with the antidepressant having the most evidence, which is fluoxetine.

24. Answer: D

Suicidal ideation is the potential adverse effect that is listed as a black box warning (Answer D is correct). The other three adverse effects are not associated with antidepressants (Answers A–C are incorrect).

25. Answer: C

Although none of the choices is FDA indicated, sertraline has the most studies showing benefit over placebo (Answer C is correct). The other choices have either not shown positive results in studies (venlafaxine and mirtazapine) (Answers A and B are incorrect) or not been studied for depression in children (bupropion) (Answer D is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: D

Although almotriptan is the only FDA label-approved medication for the acute treatment of migraines in adolescents, this patient has nausea and vomiting (Answer A is incorrect). An alternative dosing form is recommended in this case; therefore, sumatriptan would be best (Answer D is correct). Narcotics are not recommended for migraines and should be avoided, if possible (Answers B and C are incorrect).

2. Answer: C

The most likely reason for the patient's low therapeutic concentration of carbamazepine is that carbamazepine is an autoinducer (Answer C is correct). After 1 month of treatment, carbamazepine would have reduced itself. The other three choices, protein binding, displacement of the free fraction, and multi-phasal distribution, do not explain the patient's decreasing carbamazepine concentration (Answers A, B, and D are incorrect).

3. Answer: A

Of the choices, only ethosuximide is indicated for absence seizures (Answer A is correct). The other three agents are useful for generalized tonic-clonic seizures (Answers B–D are incorrect).

4. Answer: D

Baclofen is a muscle relaxer indicated for spasticity (Answer D is correct). Although the other three choices are classic symptoms of cerebral palsy, baclofen is not indicated for these symptoms and may not help relieve them (Answers A–C are incorrect).

5. Answer: B

Aripiprazole is indicated for irritability, aggression, and other tantrum-like behaviors (Answer B is correct). Aripiprazole does not improve communication skills such as following directions and verbal ability (Answers A and D are incorrect). Flat affect is also not an indication for aripiprazole and can be an adverse effect of some antipsychotics (Answer C is incorrect).

6. Answer: A

Of the choices, only olanzapine is indicated for the acute mania phase of bipolar disorder in adolescents (Answer A is correct). Lamotrigine may be helpful for

maintenance treatment or the depression phase (Answer B is incorrect). Fluoxetine is an antidepressant and is not effective for mania (Answer C is incorrect). Methylphenidate, a stimulant, is indicated for ADHD; as such, it could exacerbate this patient's manic symptoms (Answer D is incorrect).

7. Answer: B

The most common adverse effect related to initial dosing with lithium is nausea and vomiting as well as other GI problems (Answer B is correct). Leukocytosis is a potential problem with long-term lithium use (Answer A is incorrect). Pancreatitis and liver enzyme elevation are more likely to occur with valproic acid use (Answer C is incorrect). Early jitteriness and anxiety are common with SSRIs (Answer D is incorrect).

8. Answer: D

Because methylphenidate increases dopamine in the synaptic cleft, it can cause psychotic symptoms, including hallucinations and paranoia (Answer D is correct). Clonidine and guanfacine indirectly affect dopamine and are therefore less likely to cause psychotic symptoms (Answers B and C are incorrect). Atomoxetine weakly affects dopamine and is therefore less likely to cause psychotic symptoms (Answer A is incorrect).

9. Answer: A

Of the listed adverse effects, the only one associated with atomoxetine is GI discomfort (Answer A is correct). Hallucinations are associated with methylphenidate (Answer B is incorrect). Hypertension and decreased appetite are associated with atomoxetine (Answers C and D are incorrect).

10. Answer: C

Escitalopram and fluoxetine are the only two antidepressants indicated for adolescent depression (Answer C is correct). Neither venlafaxine, duloxetine, nor amitriptyline is indicated for childhood and adolescent depression, and studies comparing these medications with placebo showed no significant difference (Answers A, B, and D are incorrect). In addition, TCAs should be avoided because of the patient's overdose history (Answer D is incorrect).

11. Answer: C

This patient has serotonin discontinuation syndrome because her symptoms began only 2 days after she discontinued her medication (Answer C is correct). However, the patient may feel that this rebound depression is a result of discontinuing the medication abruptly and a return of her depression symptoms (Answer A is incorrect). She could discontinue her medication at this time, but the medication should be reduced over weeks. Serotonin syndrome occurs when several serotonergic medications are used together (Answer B is incorrect). The patient's symptoms do not reflect mania (Answer D is incorrect).

FLUIDS, ELECTROLYTES, AND NUTRITION

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Learning Objectives

1. Identify the changes in total body water, body compartments, and electrolytes during human development.
2. Interpret laboratory data and physical assessment in the evaluation of fluid status and dehydration.
3. Design intravenous fluid regimens to meet maintenance needs and to treat identified deficits based on calculated requirements.
4. Design parenteral and enteral nutrition regimens according to the changing nutrition needs and clinical status of infants and children at various stages in development.
5. Recommend appropriate therapies to manage parenteral nutrition-related complications.

Abbreviations in This Chapter

DIR/GIR	Dextrose infusion rate/ glucose infusion rate
ECF	Extracellular fluid
ED	Emergency department
ICF	Intracellular fluid
IFALD	Intestinal failure associated liver disease
ILE	Lipid injectable emulsion
ORT	Oral replacement therapy
PN	Parenteral nutrition

Self-Assessment Questions

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

Questions 1 and 2 pertain to the following case.

R.C. is a 9-year-old girl (weight 32 kg) who presents to the emergency department (ED) with complaints of generalized abdominal pain and malaise for the past 3 days, which has steadily increased during the past 24 hours such that she cannot tolerate oral intake and has a decreased appetite. She will have a workup for acute appendicitis. Physical examination reveals heart rate 133 beats/minute, respiratory rate 20 breaths/minute, and blood pressure 112/61 mm Hg.

1. The ED physician consults you for assistance in determining the appropriate maintenance fluid and rate for R.C. Which is the most appropriate recommendation?
 - A. Dextrose 10% in 0.9% sodium chloride plus potassium chloride 40 mEq/L at 108 mL/hour.
 - B. Dextrose 5% in 0.225% sodium chloride plus potassium chloride 40 mEq/L at 108 mL/hour.
 - C. Dextrose 5% in 0.9% sodium chloride plus potassium chloride 20 mEq/L at 70 mL/hr.
 - D. Dextrose 10% in 0.45% sodium chloride plus potassium chloride 40 mEq/L at 70 mL/hour.
2. Twenty-four hours after your initial fluid recommendation, R.C.'s laboratory values are as follows:

139	104	22	105
6.5	23	0.9	

The physician would like to increase the rate of the intravenous fluid to 1.5 times the maintenance rate. Which is the most appropriate recommendation?

- A. Dextrose 5% in 0.45% sodium chloride plus potassium chloride 10 mEq/L at 165 mL/hour.
- B. Dextrose 5% in 0.45% sodium chloride at 105 mL/hour.
- C. Dextrose 10% in 0.225% sodium chloride plus potassium chloride 10 mEq/L at 105 mL/hour.
- D. Dextrose 10% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 165 mL/hour.

Questions 3 and 4 pertain to the following case.

E.B., a 16-year-old female adolescent (weight 61.3 kg), presents in the ED with severe hypotension (blood pressure 65/45 mm Hg) after a snowboarding accident. She is disoriented, and her laboratory values point toward intravascular dehydration.

3. Which is the most appropriate fluid to recommend for initial resuscitation?
 - A. 25% albumin 10 mL/kg.
 - B. Dextrose 5% in 0.45% sodium chloride at 95 mL/hour.
 - C. 0.9% sodium chloride 20 mL/kg.
 - D. 5% albumin 50 mL/kg.
4. E.B. does not respond to the initial therapy in the ED. An hour after her initial presentation, her abdomen is rigid, and an emergency computed tomography (CT) scan reveals a liver laceration. Repeat laboratory tests show hematocrit 17% (previously 26%). Which is the most appropriate fluid to recommend?
 - A. 5% albumin 10 mL/kg.
 - B. Dextrose 5% in 0.45% sodium chloride at 95 mL/hour.
 - C. 0.9% sodium chloride 40 mL/kg.
 - D. Whole blood 20–30 mL/kg.

Questions 5 and 6 pertain to the following case.

E.H. is a 19-month-old boy with a 3-day history of vomiting, diarrhea, and decreased urinary output. He is given a diagnosis of gastroenteritis and dehydration. His current weight is 10 kg (previous weight was 10.45 kg). His blood pressure is stable on admission.

5. Which set of physical signs and symptoms would be most expected for his severity of dehydration?
 - A. Anuria, absent tears, capillary refill greater than 8 seconds.
 - B. Decreased skin turgor, capillary refill greater than 5 seconds, slightly increased heart rate.
 - C. Normal heart rate, slightly dry mucosa, capillary refill 2 seconds.
 - D. Normal skin turgor, capillary refill greater than 8 seconds, dry mucosa.

6. Which is the best recommendation for managing E.H.'s dehydration at this time?
 - A. Dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 70 mL/hour for 8 hours, followed by dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 56 mL/hour for 16 hours.
 - B. Dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 19 mL/hour for 24 hours.
 - C. 200 mL of 0.9% sodium chloride bolus, followed by dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 43 mL/hour for 16 hours.
 - D. 450 mL of 0.9% sodium chloride bolus, followed by dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 43 mL/hour for 24 hours.
7. S.C. is a 7-day-old term infant (weight 3.8 kg) born at 41 weeks' gestation who will receive standard infant formula. Which enteral nutrition regimen is most appropriate for S.C. to meet his caloric needs?
 - A. Enfamil (20 kcal/oz), 72 mL every 3 hours.
 - B. Similac Special Care Advance 24 (24 kcal/oz), 60 mL every 3 hours.
 - C. Enfaport (30 kcal/oz), 72 mL every 3 hours.
 - D. Similac PM 60/40 (20 kcal/oz), 60 mL every 3 hours.
8. B.B. is a 6-month-old boy (weight 6 kg) with short bowel syndrome who is parenteral nutrition (PN)-dependent. On admission, his direct bilirubin is 3.2 mg/dL, and he is found to have scleral icterus. Which is the best approach to treating B.B. at this time?
 - A. Hold PN for 48 hours.
 - B. Add cysteine 40 mg per gram of amino acid.
 - C. Decrease soybean oil based lipid emulsion dose to 1 g/kg/day or switch to fish oil based lipid emulsion 1 g/kg/day.
 - D. Add heparin 0.5 unit/mL.

9. A.J. is a 45-day-old female infant (born at term) (current weight 2.3 kg) who is receiving the following PN regimen (note: the PN infuses for 24 hours/day):

Total volume	299 mL/day
PN infusion rate	12.5 mL/hr
ILE (20%)	12 mL
Amino acids	3.4 g/kg/day
Dextrose	20.2 g/kg/day
Electrolytes	Potassium acetate (1.5 mEq/kg/day): 3.4 mEq Potassium chloride (1.8 mEq/kg/day): 4.1 mEq Sodium acetate (0.5 mEq/kg/day): 1.1 mEq Sodium chloride (2.3 mEq/kg/day): 5.2 mEq Sodium phosphate (1.2 mmol/kg/day): 2.7 mmol Magnesium sulfate (0.6 mEq/kg/day): 1.3 mEq Calcium gluconate (2.7 mEq/kg/day): 6.2 mEq
Multivitamin	3.3 mL
Trace minerals	Copper 20 mcg/kg Selenium 2 mcg/kg Zinc 250 mcg/kg
Other additives	Famotidine 0.5 mg/kg Levocarnitine 10 mg/kg

Which most accurately represents how many kilocalories per kilogram per day A.J. receives from this PN?

- A. 87.
B. 93.
C. 200.
D. 213.
10. A 9-day-old neonate (weight 1.535 kg) with congenital diaphragmatic hernia is currently NPO (nothing by mouth) and receiving PN. The PN formulation is as follows: 20% soybean-oil based lipid injectable emulsion (ILE) 23 mL (3 g/kg), Amino Acids 4% (3.5 g/kg), and dextrose 21.4% (28.7 g/day). The total volume of the PN is 134 mL, and it is infusing at a rate of 5.6 mL/hour. Which best represents the calculated dextrose infusion rate (DIR) in milligrams per kilogram per minute?
- A. 19.9.
B. 13.

- C. 17.5.
D. 14.

11. E.N. is a 7-month-old ex-31-week gestation boy with mild gastroesophageal reflux (i.e., twice weekly) who now weighs 4 kg (birth weight 1.1 kg). When plotted on standardized growth charts, he is below the 5th percentile for age and is given a diagnosis of failure to thrive. Which is the most likely risk factor for this?

- A. Early hospitalization.
B. Undiagnosed metabolic disorder.
C. Low birth weight because of prematurity.
D. Gastroesophageal reflux.

12. A 1-day-old neonate (weight 800 g), 27 weeks' gestational age, will receive PN. However, because of difficulty securing central venous access, she will receive nutrition through a peripheral venous access device. Which of the following is the most appropriate osmolarity for this patient's PN?

- A. 900 mOsm/L or less.
B. 1200 mOsm/L or less.
C. 1300 mOsm/L or less.
D. 1500 mOsm/L or less.

13. T.W. is a 23-hour-old female neonate born at 28 weeks' gestation (birth weight 1100 g). Admitted to the neonatal intensive care unit with pure esophageal atresia, she will require nutrition support. Central access is secured. Which initial nutrition support regimen is most appropriate for T.W.?

- A. Nutren Junior (1 kcal/mL) at 3.7 mL/hour via enteral feeding tube plus dextrose 10% at 1.8 mL/hour.
B. PN at 3.7 mL/hour with final dextrose concentration 10%, amino acids 4 g/kg/day, and ILE 1 g/kg/day.
C. PN at 5.5 mL/hour with final dextrose concentration 17%, amino acids 3 g/kg/day, and ILE 3 g/kg/day.
D. Similac PM 60/40 at 25 mL via enteral feeding tube every 3 hours.

BPS Pediatric Pharmacy Specialty Examination Content Outline

This chapter covers the following sections of the Pediatric Pharmacy Specialty Examination Content Outline:

1. Domain 1: Patient Management; Task(s): 1.1, 1.2, 1.3, 1.4, 1.5
2. Domain 2: Practice Management and Medication Safety; Task(s): 2.1, 2.2

I. COMPOSITION OF BODY FLUIDS

- A. Water is the largest compartment in the human body; as humans age, the percentage of total body water slowly decreases (Table 1).
- B. The ratio of extracellular fluid (ECF) to intracellular fluid (ICF) is highest during the neonatal period and decreases with increasing age (Table 1). During the neonatal period, ECF is higher than ICF. However, as these humans age into childhood, adolescence, and adulthood, ICF is higher than ECF.
- C. Water turnover rate is higher in children than in adults.

Table 1. Estimates of Human Composition Across the Age Spectrum

	Premature Neonate	Term Neonate	Infant	Child	Adolescent/Adult
Total body water (%)	85	75	60–70	60	50–60
Extracellular fluid (%)	70	70	55	40	33.3
Intracellular fluid (%)	30	30	45	60	66.7

II. TYPES OF INTRAVENOUS FLUID

- A. Crystalloids – Indicated for most conditions and the mainstay of intravenous fluid therapy (Table 2)
 1. Dextrose-containing fluids
 2. Saline-containing fluids
 3. Lactated Ringer solution
- B. Colloids – Indicated in specific conditions such as capillary leak, third spacing, nephrotic syndrome/hypoproteinemia, malnourished states, excessive blood loss, volume expansion
 1. Albumin
 2. Blood
 3. Hetastarch and pentastarch
 4. Dextran

Table 2. Content of Crystalloid Fluids

Fluid	Osmolality (mOsm/L)	Sodium (mEq/L)	Chloride (mEq/L)	Other
Dextrose 5% (D5W) only	252	—	—	
0.9% sodium chloride (NaCl)	308	154	154	
0.45% NaCl	154	77	77	
0.225% NaCl ^a	77	38.5	38.5	
Lactated Ringer solution	273	130	109	Potassium 4 mEq/L, lactate 28 mEq/L, calcium 3 mg/dL
PlasmaLyte ^b	294	140	98	Potassium 5 mEq/L, magnesium 3 mEq/L, acetate 27 mEq/L, gluconate 23 mEq/L

^aNote: 0.225% NaCl cannot be infused alone; it must be co-infused with a dextrose-containing solution. When infused alone, 0.225% NaCl may cause cell lysis, which may lead to hyperkalemia, cardiac arrhythmias, and death.

^bNote: Generic name for PlasmaLyte is multiple electrolytes injection, type 1, USP.

III. MAINTENANCE FLUIDS AND ELECTROLYTES

A. Goals of Maintenance Intravenous Fluid Therapy

1. To prevent dehydration, electrolyte disturbances, ketoacidosis, and protein degradation as well as maintain euglycemia
2. To maintain fluid balance in the body and replace ongoing normal losses (e.g., insensible, urine, and fecal losses) (Table 3)

Table 3. Ongoing Loss Across the Pediatric Age Spectrum

	Insensible (mL/kg/day)	Urine (mL/kg/day)	Fecal (mL/kg/day)
Neonate to 6 mo	40	60	20
6 mo to 5 yr	30	60	10
5–10 yr	20	50	Variable
Adolescent	10	40	Variable

3. Maintenance fluids do not provide adequate calories, fat, protein, minerals, or vitamins for normal growth and development of children.

B. Main Components of Maintenance Intravenous Fluid Therapy

1. Water
2. Sodium
3. Potassium
4. Dextrose

Note: Supplements such as calcium, magnesium, and phosphorus are not routinely added to maintenance fluid therapy. However, some providers may consider adding calcium to maintenance intravenous fluids for neonates. Preterm neonates typically require calcium in maintenance intravenous fluids.

C. Guiding Principles

1. No two patients are exactly alike; therapy must be individualized.
2. Calculations are only estimates; the patient's clinical condition dictates the therapeutic course, and adjustments should be made according to the patient's individual needs.
3. Maintenance fluids and electrolytes are needed to account for normal losses from basal metabolism.
 - a. Metabolic rate is higher (kcal/kg of body weight) in younger patients than in older patients.
 - b. Metabolic rate declines with increasing age.
4. Several estimates of maintenance fluid needs exist, including surface area method (may underestimate needs/be inaccurate when weight is less than 10 kg), basal caloric method (most accurate, but less practical), and estimations using weight. Estimations of maintenance needs using body weight are the most clinically practical, but they may overestimate the needs.

D. Estimates of Maintenance Fluid Needs Using Body Weight (Table 4 and Table 5)

1. Holliday-Segar method (provides estimates over a 24-hour period) – Assumes that 100 calories are metabolized for each 100 mL of water required
2. 4-2-1 method (provides estimates over an hourly period; may underestimate needs)

Table 4. Estimation of Maintenance Fluid Requirements Using Body Weight for Infants and Children

Body Weight (kg)	Holliday-Segar (24-hour requirement)	4-2-1 (hourly requirement)
0–10	100 mL/kg	4 mL/kg/hr
> 10–20	1000 mL plus 50 mL/kg for each kg > 10 kg to ≤ 20 kg	40 mL/hr plus 2 mL/kg/hr for each kg > 10 kg to ≤ 20 kg
> 20	1500 mL plus 20 mL/kg for each kg > 20 kg	60 mL/hr plus 1 mL/kg/hr for each kg > 20 kg

Table 5. Estimation of Maintenance Fluid Requirements Using Body Weight for Neonates

< 1500 g	70–160 mL/kg/day *depending on clinical status
1500–2000 g	60–140 mL/kg/day *depending on clinical status
Term neonate	80–150 mL/kg/day *depending on clinical status

E. General Maintenance Requirements of Electrolytes

Needs may be higher/lower depending on age as well as clinical status.

1. Sodium: 2–5 mEq/kg/day
2. Chloride: 3–5 mEq/kg/day
3. Potassium: 1–2 mEq/kg/day

F. Using General Maintenance Requirements of Electrolytes – Standard intravenous fluids used in pediatric patients include

1. Newer data identify a risk of hyponatremia with the use of hypotonic intravenous fluids.
 - a. Specific clinical situations should be considered when choosing intravenous fluid.
 - b. Isotonic intravenous fluids (e.g., 0.9% sodium chloride-containing fluids, lactated Ringer solution) may be preferred in acutely ill, hospitalized patients.
2. Dextrose 5% in 0.225% sodium chloride plus potassium chloride 20 mEq/L
Use cautiously in critically ill children; dextrose 5% in 0.225% sodium chloride may lead to hyponatremia in the critically ill child because fluid and electrolyte requirements are not the same as in an otherwise healthy individual. As a result of this newer data, many institutions and practitioners no longer use this fluid routinely.
3. Dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L
Use cautiously in critically ill children; dextrose 5% in 0.45% sodium chloride may lead to hyponatremia in the critically ill child because fluid and electrolyte requirements are not the same as in an otherwise healthy individual. As a result of this newer data, many institutions and practitioners no longer use this fluid routinely.
4. Neonates
 - a. First 24–48 hours of life: Dextrose 10%
 - i. Neonates require more dextrose to maintain euglycemia.
 - ii. Electrolytes (e.g., Na⁺ and K⁺) are typically avoided in the first 24–48 hours of life to allow a physiologic period of diuresis (Na⁺ and water) to occur and because of immature renal function (K⁺).
 - b. Greater than 48 hours of life: Dextrose 10% in 0.225% sodium chloride

G. Select Conditions That Increase Maintenance Fluid Requirements

1. Phototherapy/radiant warmers
2. Fever
3. Increased sweating
4. Hyperventilation/hypermotabolic state
5. Inability of kidneys to conserve water
6. Vomiting/nasogastric suctioning
7. Intestinal losses
8. Gastroschisis/omphalocele

H. Select Conditions That Decrease Maintenance Fluid Requirements

1. Mist tents/humidified environment
2. Endotracheal intubation
3. Respiratory distress syndrome
4. Decreased renal function
5. Hypometabolic state

Patient Cases

Questions 1 and 2 pertain to the following case.

J.H. is a 9-year-old boy (weight 35 kg) who has had generalized abdominal pain, localized to the right lower quadrant, and malaise for the past 4 days. He has been unable to tolerate any oral intake because of persistent nausea and vomiting, and his appetite is decreased. He now presents to the ED, where he will be evaluated for acute appendicitis. On examination, the patient feels warm to the touch. His initial temperature on admission was 97.7°F (36.5°C). However, in the ED, his temperature increased to greater than 101.3°F (38.5°C). His heart rate is 130 beats/minute, respiratory rate is 32 breaths/minute, and blood pressure is 111/60 mm Hg, with pulse oximetry 96%.

Laboratory values:

137	104	33	102	~~11.4~~ 15.4 33.8	336	Ca: 10.4 mg/dL
4.1	23	0.4				

1. Which most accurately reflects J.H.'s maintenance fluid needs using the Holliday-Segar method?
 - A. 700 mL/day; 29.2 mL/hour.
 - B. 1800 mL/day; 75 mL/hour.
 - C. 840 mL/day; 35 mL/hour.
 - D. 1500 mL/day; 62.5 mL/hour.
2. According to J.H.'s laboratory values, which maintenance intravenous fluid would be best to recommend?
 - A. Dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L.
 - B. Dextrose 10% plus potassium chloride 10 mEq/L.
 - C. Dextrose 5% in 0.225% sodium chloride.
 - D. Dextrose 10% in 0.45% sodium chloride plus potassium chloride 20 mEq/L.

I. Additional and Ongoing Losses

1. If the patient has an additional source of loss (e.g., chest tube, gastrostomy tube), maintenance fluid requirements should account for these additional losses.
2. Consider these types of losses separately from maintenance and deficit requirements.
3. Choice of fluid therapy is determined according to the type of ongoing loss.
 - a. Most precise: Volume and concentration of electrolyte losses should be measured to aid in fluid choice.
 - b. Practical: Reference tables (Table 6) aid in fluid choice.

Table 6. Approximate Electrolyte Composition of Body Fluids

	Gastric	Pancreatic	Small Bowel	Bile	Ileostomy	Diarrhea	Burns	Sweat
Na (mEq/L)	20–80	120–140	100–140	120–140	45–135	10–90	140	10–30
K (mEq/L)	5–20	5–15	5–15	5–15	3–15	10–80	5	3–10
Cl (mEq/L)	100–150	90–120	90–130	80–120	20–115	10–110	110	10–35

Cl = chloride; K = potassium; Na = sodium.

Patient Case

3. J.G., a 5-year-old boy with a history of bilateral renal artery stenosis complicated by renovascular hypertension and fibromuscular dysplasia, underwent bilateral renal artery-reimplantation, superior mesenteric artery bypass, and patch aortoplasty. He presents to the ED today and is admitted for concern of possible bowel obstruction secondary to poor appetite, no stools for 48 hours, and nausea/vomiting for 3 days. A nasogastric tube is placed, and on placement, copious bilious fluid is suctioned from his stomach. Which fluid is best to replace J.G.'s ongoing losses?
 - A. Dextrose 5% in 0.45% sodium chloride.
 - B. 0.9% sodium chloride.
 - C. 0.45% sodium chloride.
 - D. Dextrose 5% in 0.9% sodium chloride.

IV. DEHYDRATION

A. General Principles of Dehydration

1. Leading cause of morbidity and mortality
2. Dehydration occurs when intake of fluids and electrolytes is less than the combined normal and abnormal losses.
3. Main causes of dehydration in the United States are diarrhea, gastroenteritis, febrile illness, diabetic ketoacidosis, excessive heat, burns, and inability to match intake with ongoing losses.
4. Dehydration occurs more quickly in neonates/infants (i.e., within 4–6 hours) because of higher insensible losses than in older children (12–18 hours).
5. Source of loss
 - a. Dehydration for less than 3 days: ECF 80%, ICF 20%
 - b. Dehydration for 3–6 days: ECF 60%, ICF 40%
 - c. Dehydration for more than 6 days: ECF 50%, ICF 50%

B. Clinical Evaluation and Assessment of Severity

1. Assessment

- a. Age, weight change, concurrent diseases, quantification of recent fluid intake and losses, skin turgor, mucous membranes, fontanelle, cardiovascular status, neurologic state, serum electrolytes, whole blood measurements, urinary output
- b. Physical examination
 - i. First sign of mild dehydration is tachycardia, which can progress to hypotension in severe dehydration.
 - ii. Skin is a reliable organ to assess dehydration (turgor, temperature, capillary refill).

2. Classification of dehydration severity (Table 7)

- a. Estimation of severity of dehydration calculation

- i. Severity of dehydration

$$\text{Severity of dehydration (\%)} = \frac{\text{pre-illness weight (kg)} - \text{illness weight (kg)}}{\text{pre-illness weight (kg)}} \times 100$$

- ii. Fluid deficit

$$\text{Fluid deficit (L)} = \frac{\% \text{ dehydration} \times \text{pre-illness weight (kg)}}{100}$$

- b. Mild dehydration

- i. Infants: 1%–5%
 - ii. Children: 1%–3%

- c. Moderate dehydration

- i. Infants: 6%–10%
 - ii. Children: 4%–6%

- d. Severe dehydration

- i. Infants: Greater than 10% (greater than 15% = shock)
 - ii. Children: Greater than 6% (greater than 9% = shock)

Table 7. Signs and Symptoms of Dehydration: Categorized by Severity

	Mild	Moderate	Severe
Pulse	Full, normal rate	Slightly increased	Rapid, weak
Systolic BP	Normal	Normal-low	Shock
Urine output	Normal or decreased	Markedly decreased	Anuric
Weight loss	3%–5%	6%–10%	>10%–15%
Thirst	Slight	Moderate	Intense
Mucosa	Normal/slightly dry	Dry	Extremely dry
Tears	Present	Reduced	Absent
Eyes	Normal	Deep set	Markedly sunken
Skin turgor	Normal	Decreased	Tenting/increased
Skin temperature	Normal	Cool	Cool/mottling
Fontanelle	Flat	Reduced	Sunken
Capillary refill	2–3 s	> 5 s	> 8 s
Behavior	Normal	Irritable	Irritable/lethargic

Patient Case

Questions 4 and 5 pertain to the following case.

K.K. is a 3-year-old girl admitted to the hospital with a 3-day history of severe diarrhea. On admission, she weighs 15 kg; however, her caregiver reports that she usually weighs 15.8 kg.

4. Which best describes K.K.'s percentage of dehydration and classification of dehydration?
 - A. 5%; moderate.
 - B. 8%; severe.
 - C. 8%; moderate.
 - D. 5%; mild.
5. Which best describes K.K.'s fluid deficit?
 - A. 790 mL.
 - B. 750 mL.
 - C. 75 mL.
 - D. 79 mL.

C. Management of Dehydration

1. Oral rehydration therapy (ORT) (preferred for mild and moderate dehydration)
 - a. Less expensive, more convenient, and can be implemented in a variety of settings
 - b. Commercial products available (e.g., Pedialyte), which contain appropriate electrolytes for rehydration
 - c. Discourage use of juices, ginger ale, sodas, sports drinks, and broths because they do not contain the appropriate electrolytes for rehydration and their high carbohydrate content may worsen diarrhea and dehydration.
 - d. Dosing ORT
 - i. Mild dehydration
 - (a) 50 mL/kg of ORT plus 10 mL/kg for every stool or emesis during 4 hour period
 - (b) Reassess every 2 hours.
 - ii. Moderate dehydration
 - (a) 100 mL/kg of ORT plus 10 mL/kg for every stool or emesis during 4 hour period
 - (b) Reassess every hour.

Patient Case

6. A mother has called the pharmacy for a recommendation for an ORT for her 5-year-old son (weight 20 kg), who currently has a mild case of nausea, vomiting, and diarrhea. Which is the most appropriate recommendation?
 - A. Gatorade 50 mL/hour for each stool or emesis.
 - B. Pedialyte 100 mL/kg plus 10 mL/kg for each stool or emesis.
 - C. Initiation of loperamide 0.08–0.24 mg/kg/day divided into three daily doses.
 - D. Pedialyte 50 mL/kg plus 10 mL/kg for every stool or emesis.

2. Intravenous rehydration therapy (indicated for moderate to severe dehydration)
 - a. Indications
 - i. Failure after ORT trial

- ii. Severe dehydration/shock
- iii. Intractable vomiting/excessive stool loss
- iv. Acute abdomen
- v. Coma
- vi. Age younger than 3 months or weight less than 4.5 kg
- vii. Severe electrolyte abnormalities
- b. Phases of intravenous replacement
 - i. Phase 1: Emergency phase
 - (a) Goals: Maintain adequate intravascular volume, maintain hemodynamics, prevent organ damage
 - (b) Approach: Bolus 10–20 mL/kg of isotonic (e.g., 0.9% sodium chloride, lactated Ringer solution) or colloid (e.g., blood, 5% albumin) administered over 15–30 minutes

Patient Case

Questions 7 and 8 pertain to the following case.

S.B., a 13-year-old girl (weight 55 kg) who presents to the ED after a motor vehicle accident, has severe hypotension (60/40 mm Hg). She is lethargic and has the following signs on physical examination: rapid heart rate (180 beats/minute) and delayed capillary refill (10 seconds).

7. Which is the best initial therapy for S.B.?
 - A. Dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 92 mL/hour.
 - B. Dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 1000 mL/hour for 1 hour.
 - C. 0.9% sodium chloride at 92 mL/hour.
 - D. 0.9% sodium chloride at 2000 mL/hour for 30 minutes.
8. S.B. is unresponsive to two 0.9% sodium chloride boluses, and her abdomen is found to be rigid. An emergency CT scan reveals a large hematoma in her abdomen. Subsequently, her hematocrit is 19%, and her blood pressure remains at 60/40 mm Hg. Which therapy would be best to recommend at this time?
 - A. 0.9% sodium chloride at 1000 mL/hour for 1 hour.
 - B. Whole blood at 20 mL/kg.
 - C. 0.9% sodium chloride at 92 mL/hour.
 - D. Lactated Ringer solution at 92 mL/hour.

- ii. Phase 2: Maintenance phase/deficit management
 - (a) Goals: Maintain perfusion, correct electrolyte imbalances, keep up with ongoing losses and maintenance requirements
 - (b) Approach:
 - (1) Calculate replacement therapy (milliliter deficit).
 - (2) Calculate maintenance fluid and electrolyte therapy.
 - (3) Consider ongoing losses. Note: Determining the patient's sodium status is important for choosing the appropriate fluid (see section V. Sodium Homeostasis).
 - c. End points of therapy – Normalize blood pressure, urinary output and specific gravity, serum electrolytes, clinical signs/symptoms of dehydration

V. SODIUM HOMEOSTASIS

- A. Calculation of Fluid Deficit (section IV.B.2.a.ii)
- B. Three Main Types of Dehydration: Isonatremia, hypernatremia, and hyponatremia. Table 8 details these and the therapeutic approach to each.
- C. Isonatremic Dehydration
 - 1. Step 1: Calculate fluid deficit.
 - 2. Step 2: Calculate sodium deficit.

$$\text{Sodium deficit} = \text{Fluid deficit (L)} \times 0.6 \frac{\text{L}}{\text{kg}} \times \text{normal sodium concentration } (135 \frac{\text{mEq}}{\text{L}})$$

- 3. Step 3: Choose intravenous solution (usually dextrose 5% in 0.45% sodium chloride [plus or minus potassium, depending on potassium deficit]).
 - a. To calculate potassium deficit

$$\text{potassium deficit} = \text{fluid deficit (L)} \times 0.4 \frac{\text{L}}{\text{kg}} \times 120 \text{ mEq/L}$$

- b. Give only half of replacement over the first 8 hours, and give the second half over the remaining 16 hours.

D. Hypernatremic

- 1. Step 1: Calculate fluid deficit.
- 2. Step 2: Calculate sodium deficit.
 - a. FWD (free water deficit) = $4 \text{ mL} \times (\text{actual sodium} - \text{desired sodium } [140 \text{ mEq/L}]) \times \text{body weight (kg)}$
 - b. Next, calculate solute fluid deficit (SFD): $\text{SFD} = \text{fluid deficit} - \text{FWD}$
 - c. Next, calculate sodium deficit

$$\text{Sodium deficit} = \text{SFD (L)} \times 0.6 \frac{\text{L}}{\text{kg}} \times \text{normal sodium concentration } (140 \frac{\text{mEq}}{\text{L}})$$

- 3. Step 3: Choose intravenous solution (usually dextrose 5% in 0.225% sodium chloride [plus or minus potassium, depending on potassium deficit])
 - a. To calculate potassium deficit

$$\text{potassium deficit} = \text{SFD (L)} \times 0.4 \frac{\text{L}}{\text{kg}} \times 120 \text{ mEq/L}$$

- b. Give only one-half of the replacement over first 24 hours and remaining one-half over the next 48–72 hours

E. Hyponatremic

- 1. Step 1: Calculate fluid deficit.
- 2. Step 2: Calculate sodium deficit.

$$\text{Sodium deficit} = \text{Fluid deficit (L)} \times 0.6 \frac{\text{L}}{\text{kg}} \times \text{normal sodium concentration } (140 \frac{\text{mEq}}{\text{L}})$$

- 3. Step 3: Calculate excess sodium deficit.

$$(\text{desired sodium } (135 \frac{\text{mEq}}{\text{L}}) - \text{actual serum sodium}) \times \text{body weight (kg)} \times 0.6 \text{ L/kg}$$

- 4. Step 4: Calculate total sodium deficit (= sodium deficit + excess sodium deficit).

5. Step 5: Choose intravenous solution (usually, dextrose 5% in 0.45% sodium chloride or dextrose 5% in 0.9% sodium chloride [plus or minus potassium, depending on potassium deficit]).
 - a. To calculate potassium deficit
$$\text{potassium deficit} = \text{fluid deficit (L)} \times 0.4 \frac{\text{L}}{\text{kg}} \times 120 \text{ mEq/L}$$
 - b. Give only one-half of the replacement over first 8 hours and remaining one-half over next 16–72 hours.
 - c. Special consideration for neurologic symptoms/acute management:
 - i. If serum sodium is less than 130 mEq/L, clinical signs and symptoms of neurologic compromise may be present.
 - ii. When serum sodium falls below 120 mEq/L, seizures may occur.
 - iii. Replace deficits using isotonic or hypertonic saline, depending on clinical severity and etiology (e.g., 0.9% sodium chloride = sodium 154 mEq/L, 3% sodium chloride = sodium 513 mEq/L).
 - (a) Dose (mEq sodium) = [desired sodium (mEq/L) – actual serum sodium (mEq/L)] $\times$ 0.6 $\times$ wt (kg).
 - (b) For acute correction, use 125 mEq/L as the desired serum sodium.
 - (c) Hypertonic saline: Administration through a central line is preferred to avoid venous irritation and infiltration (3% sodium chloride has a high osmolality [e.g., greater than 1000 mOsm/L]).
 - (d) If using 3% sodium chloride, each 4-mL/kg increases the serum sodium by around 1 mEq/L.
 - (e) Rate of correction: Acutely correct by 5mEq/L/dose increments not to exceed 2 mEq/L/hour initially; then correct at a rate of 0.5 mEq/L/hour. Do not exceed a correction of 12 mEq/L/day.

Table 8. Disorders of Sodium and Water Homeostasis

Isonatremic (isotonic)	Hypernatremic (hypertonic)	Hyponatremic (hypotonic)
Most common type (80%)	Second most common type	Least common type
Serum sodium concentration and osmolality near normal (130–150 mEq/L)	Serum sodium concentration and osmolality above normal (> 150 mEq/L and > 300 mOsm/L)	Serum sodium concentration and osmolality below normal (< 130 mEq/L and < 260 mOsm/L)
Water and electrolyte losses equal to those found in ICF and ECF	Water losses exceed salt losses	Salt losses exceed water losses
Examples: • Diarrhea • Decreased intake	Examples: • Diabetes insipidus	Examples: Euvolemia: • Syndrome of inappropriate antidiuretic hormone (SIADH), administration of hypotonic fluid Hypovolemia: • Gastroenteritis, loop diuretics Hypervolemia: • Edema, heart failure, cirrhosis, nephrotic syndrome
• Replace 50% deficit over first 8 hr • Replace remaining 50% over next 16 hr	• Replace 50% deficit over first 24 hr • Replace remaining 50% over the next 48–72 hr • Correction of sodium should not exceed 12 mEq/L per 24 hr	• Avoid rapid correction • Replace 50% deficit over first 8 hr • Replace remaining 50% over the next 16–72 hr • Correction of sodium should not exceed 12 mEq/L per 24 hr
Usually require Na 8–10 mEq/kg and K ~4 mEq/kg	Usually require Na 2–4 mEq/kg and K ~0–4 mEq/kg	Usually require Na 10–12 mEq/kg and K ~4 mEq/kg

Box 1. Example – Hyponatremic Dehydration

A 2-month-old infant presents to the ED with a 3-day history of projectile vomiting and is given a diagnosis of pyloric stenosis. The infant appears physically dehydrated and has a serum sodium of 129 mEq/L. Pre-illness weight is 5 kg; current weight on admission is 4.8 kg. Vital signs are stable.

Determine the appropriate fluid and rate.

Calculation of Deficits

Step 1: Calculate fluid deficit.

$$\begin{aligned}\% \text{ dehydration} &= (5 \text{ kg} - 4.8 \text{ kg}) / 5 \text{ kg} \times 100 \\ &= 4\%\end{aligned}$$

$$\begin{aligned}\text{Fluid deficit} &= 0.04 \times 5 \text{ kg} \\ &= 0.2 \text{ L (200 mL)}\end{aligned}$$

Step 2: Calculate sodium deficit.

$$\begin{aligned}\text{Sodium deficit} &= 0.2 \text{ L} \times 0.6 \text{ (L/kg)} \times 140 \text{ mEq/L} \\ &= 16.8 \text{ mEq}\end{aligned}$$

$$\begin{aligned}\text{Excess sodium deficit} &= (135 \text{ mEq/L} - 129 \text{ mEq/L}) \times 0.6 \text{ (L/kg)} \times 5 \text{ kg} \\ &= 18 \text{ mEq}\end{aligned}$$

$$\text{Total sodium deficit} = 18 \text{ mEq} + 16.8 \text{ mEq} = 34.8 \text{ mEq}$$

Step 3: Calculate potassium deficit.

$$\begin{aligned}\text{Potassium deficit} &= 0.2 \text{ L} \times 0.4 \text{ (L/kg)} \times 120 \text{ mEq/L} \\ &= 9.6 \text{ mEq}\end{aligned}$$

Calculation of Maintenance Needs

$$\text{Fluid needs: } 5 \text{ kg} \times 100 \text{ mL/kg} = 500 \text{ mL}$$

$$\text{Sodium needs: } 3 \text{ mEq/kg} \times 5 \text{ kg} = 15 \text{ mEq}$$

$$\text{Potassium needs: } 2 \text{ mEq/kg} \times 5 \text{ kg} = 10 \text{ mEq}$$

(Note: Fluid needs calculated using the Holliday-Segar method; sodium needs around 2–5 mEq/kg/day; potassium needs around 1–2 mEq/kg/day, see sections III.E.1. and III.E.3., respectively)

Replacement:

A. First 8 hr, give 50% of deficit needed plus 33.3% of maintenance needs.

a. Volume = $(0.5 \times 200 \text{ mL}) + (0.333 \times 500 \text{ mL}) = 267 \text{ mL}$

b. Sodium = $(0.5 \times 34.8 \text{ mEq}) + (0.333 \times 15 \text{ mEq}) = 22.4 \text{ mEq}$

c. Potassium = $(0.5 \times 9.6 \text{ mEq}) + (0.333 \times 10 \text{ mEq}) = 8 \text{ mEq}$

Dextrose 5% in 0.45% sodium chloride plus potassium 20 mEq/L at 33 mL/hr × 8 hr

(Note: This fluid will provide 20 mEq of sodium and 5 mEq of potassium [close to goal].)

B. Next 16 hr, give 50% of deficit needed plus 66.7% of maintenance needs.

a. Volume = $(0.5 \times 200 \text{ mL}) + (0.667 \times 500 \text{ mL}) = 433 \text{ mL}$

b. Sodium = $(0.5 \times 34.8 \text{ mEq}) + (0.667 \times 15 \text{ mEq}) = 27.4 \text{ mEq}$

c. Potassium = $(0.5 \times 9.6 \text{ mEq}) + (0.667 \times 10 \text{ mEq}) = 11.5 \text{ mEq}$

Dextrose 5% in 0.45% sodium chloride plus potassium 30 mEq/L at 27 mL/hr × 16 hr

(Note: This fluid will provide 33 mEq of sodium and 13 mEq of potassium [close to goal].)

VI. NUTRITION ASSESSMENT

- A. Growth – Should be routinely monitored in healthy and hospitalized infants and children
- B. Measurements of Growth – Plotted on growth curves (e.g., Centers for Disease Control and Prevention, World Health Organization) and expressed as percentiles for age (Fenton growth charts exist for preterm infants at 22–50 weeks' gestational age)
 - 1. Weight
 - 2. Length/height
 - 3. Head circumference (typically used until 3 years of age)
- C. Additional Measurements – Can be used to assess nutrition
 - 1. Triceps skinfold thickness
 - 2. Mid-arm circumference
 - 3. Handgrip strength
 - 4. Food and nutrition history
 - 5. Anthropometrics
 - 6. Biochemical data/medical tests and procedures
 - 7. Nutrition focused physical exam
 - 8. Documentation of Tanner Stage
- D. Nutritional Needs of Pediatric Patients – Increased per kilogram compared with adults
- E. Pediatric Patients Have Reduced Nutritional Reserves – Prematurity predisposes pediatric patients to nutritional deficits because most nutritional maturation occurs during the third trimester of gestation.
- F. Growth Velocity
 - 1. Greatest during the first few months of life
 - a. Preterm neonate should gain 10–15 g/kg/day.
 - b. Neonates and infants should gain 20–30 g/day (double birth weight by about 4 months of life).
 - c. 2–10 years of life: Children gain 2–3 kg per year.
 - 2. Length increases by around 50% during the first year; older children grow 2.5–3.5 inches per year.

VII. CALORIC REQUIREMENTS

- A. Table 9 – Describes the typical caloric requirements across the pediatric age spectrum
- B. Determinant Factors of Specific Nutritional and Caloric Needs in Pediatric Patients
 - 1. Growth rate and stage of growth
 - 2. Body size
 - 3. Base energy expenditure
 - 4. State of health and illness
 - 5. Physical activity

Table 9. Typical Caloric Requirements Across the Pediatric Age Spectrum

Age	Caloric Requirement (kcal/kg/day)
Premature neonate	90–120
Term neonate	100–110
Infant	80–110
Child	70–90
Adolescent	40–60

VIII. ENTERAL NUTRITION

- A. Administration of Nutrition to the Gastrointestinal (GI) Tract – Typically, through a gastrostomy or jejunostomy tube and/or a nasogastric, orogastric, nasojejunal, or orojejunal tube, though may be given orally as well
- B. Indications
 1. Prematurity before suck-swallow reflex (less than 32–34 weeks' gestational age)
 2. Critical illness/mechanical ventilation unable to meet needs by mouth
- C. Methods of Delivery
 1. Bolus/intermittent infusion
 2. Continuous infusion
 3. Cycled infusion
- D. Types of Enteral Nutrition
 1. Breast milk (exclusive breast milk is recommended for the first 6 months of life)
 - a. Expressed breast milk can be given to neonates and infants through enteral feeding tubes for those who cannot breastfeed.
 - b. Donor breast milk available in some institutions
 - c. Advantages to breast milk (child)
 - i. Decreased rate of upper respiratory infections (i.e., otitis media), urinary tract infections, necrotizing enterocolitis, and other infections
 - ii. Decreased rate of sudden infant death syndrome
 - iii. Decreased incidence of allergy, asthma, cancer, diabetes, and obesity
 - d. Advantages to breast milk (mother)
 - i. Less postpartum bleeding
 - ii. Uterus returns to normal size faster after delivery
 - iii. Decreases risk of certain types of cancers (e.g., ovarian, breast)
 - iv. Improves weight loss after pregnancy
 - v. Improves bone remineralization
 - vi. Maternal bonding
 - e. Human milk composition (typically around 20 kcal/oz)
 - i. Varies between women/diet
 - ii. Varies depending on the stage of lactation
 - iii. Varies depending on the time of day and time into feeding

- f. Stages of human milk
 - i. Colostrum (milk produced during first several days after delivery)
 - (a) Rich in antibodies
 - (b) Lower in fat and energy than mature milk
 - (c) Higher in protein, fat-soluble vitamins, minerals, and electrolytes than mature milk
 - (d) Easier to digest (higher whey/casein ratio)
 - ii. Transitional milk (milk that is produced on days 3–14 after delivery)
 - iii. Mature milk (milk that is produced 2 weeks after delivery)
- 2. Infant formulas (available for feeding infants whose mothers cannot breastfeed and/or provide expressed breast milk)
 - a. Many types of enteral formulas
 - i. Ready-to-feed
 - ii. Dry powders
 - iii. Concentrated liquids
 - b. Choosing the right formula
 - i. Patient-specific factors
 - (a) Age
 - (b) Nutritional requirements
 - (c) Level of activity
 - (d) Failure to thrive
 - (e) GI function
 - ii. Formula-specific factors
 - (a) Nutrient composition
 - (b) Osmolality
 - (c) Renal solute load
 - (d) Caloric density
 - (e) Cost and availability
 - iii. Other factors
 - (a) Route of feeding
 - (b) Family/lifestyle concerns
 - c. Standard formulas provide 20 kcal/oz.
 - d. Premature formulas provide 22–24 kcal/oz.
 - e. Caloric density may be altered by providing protein, carbohydrate, or fat source modular additive.
- 3. Select formulas for special medical conditions
 - a. Nutramigen
 - i. Amino acid–based, hypoallergenic formula
 - ii. Designed for infants with severe cow’s milk allergy or several food allergies
 - b. Enfaport
 - i. Increases medium-chain triglycerides to bypass the lymphatic system
 - ii. Used for infants with chylothorax
 - iii. May lead to essential fatty acid deficiency
 - c. Neocate
 - i. Completely elemental formula
 - ii. Designed for infants with severe allergies or GI dysfunction
 - d. EleCare
 - i. Completely elemental formula
 - ii. Designed for infants with severe allergies/GI dysfunction
 - iii. Increased percentage of medium-chain triglycerides compared with Neocate

- e. Similac PM 60/40
 - i. Infants with renal function or cardiovascular disease
 - ii. Decreased potassium, calcium, and phosphorus
- f. Special formulas
 - i. MSUD (maple syrup urine disease)
 - ii. PKU (phenylketonuria)
 - iii. Urea cycle disorders

Patient Case

9. C.G. is a term neonate (weight 3.2 kg) with a caloric goal of 100 kcal/kg/day. She is receiving breast milk, and she feeds eight times per day. Which is the best volume (milliliters) that C.G. must consume at each feed to meet her caloric goals for the day?
- A. 60 mL per feed.
 - B. 27 mL per feed.
 - C. 160 mL per feed.
 - D. 40 mL per feed.

- 4. Toddler formulas for older children (9–24 months of age)
 - a. Standard formulas provide 20 kcal/oz.
 - b. Marketed as nutritious alternatives to whole cow's milk to promote growth
 - c. Contain increased amounts of vitamins C and E and iron
- 5. Formulas for children 1–10 years of age
 - a. Indicated for children with special medical conditions when caloric needs cannot be met with typical oral diet
 - b. Examples
 - i. Lactose-free formulas
 - ii. Formulas with or without fiber
 - iii. Cow's milk-based formulas
 - iv. Hydrolyzed, semi-elemental or completely elemental formulas
 - v. Blenderized, real food or whole-food feeding formulas. Note: Some blenderized, real-food, or whole-food formulas may be high in certain nutrients such as vitamin A, which may necessitate monitoring.

E. Initiation and Advancement of Enteral Nutrition

- 1. Breastfeeding
 - a. Should begin within the first hours after delivery (unless medical contraindications)
 - b. Feedings should be on demand; frequency may vary depending on the individual child's needs.
 - i. Usually about 8–12 times/day for first 2 weeks
 - ii. 7–9 times daily by 4 weeks of age. Difficult to know exactly how much child is taking during each feed; therefore, appropriate growth should be used as a measurement of adequate nutrient intake
 - c. Recommended to provide vitamin D 400 IU daily during breastfeeding.
- 2. Infant formula
 - a. Initiation depends on infant's medical status.
 - b. If healthy, initiation can occur almost immediately
 - i. Usually 1–2 oz every 3 hours, with advancement to meet nutritional needs
 - ii. Most infants will eat on demand.
 - c. If medical complications, slow advancement will occur until nutritional goals are reached

F. Formula Additives

1. Docosahexaenoic acid
 - a. Important for neurologic development (normally found in human milk)
 - b. Synthesized from essential fatty acid α -linolenic acid
 - c. Large quantities of docosahexaenoic acid found in the brain and retina
 - d. Highest concentration found in the photoreceptor membrane of the retina
2. Arachidonic acid
 - a. Required for optimal growth (normally found in human milk)
 - b. Synthesized from essential fatty acid linoleic acid
3. Probiotics/prebiotics: Support healthy immune systems
4. Iron
 - a. Critical for growth and development
 - b. Most infant formulas provide elemental iron at around 2 mg/kg/day.
5. Others
 - a. Dry rice cereal – Usually added as thickener for babies with reflux or difficulty swallowing thin liquids
 - b. Polycose Powder – Increased carbohydrate content and caloric density
 - c. MCT oil – Medium-chain fatty acids increase caloric density
 - d. ProMod – Increased protein content and caloric density

G. Medication-Nutrient Considerations

1. Avoid administering enteric-coated or extended-release products by enteral feeding devices.
2. Immediate-release products, solutions, and suspensions must be carefully evaluated to verify their ability to administer by enteral feeding device.
3. Site of absorption must also be considered when administering medications through enteral feeding devices (i.e., gastric vs. jejunal).
4. Avoid mixing medications directly with enteral formula; rather, administer separately, and flush enteral feeding device well after administration to avoid interactions.

H. Complications of Enteral Nutrition

1. Mechanical obstruction of enteral feeding device
2. Tubing misconnections
3. Oral aversion

IX. PARENTERAL NUTRITION: DELIVERY OF NUTRITION DIRECTLY INTO THE BLOODSTREAM THROUGH VENOUS ACCESS DEVICES**A. Indications**

1. Cannot meet nutritional needs by oral or enteral route
2. Nonfunctioning GI tract (e.g., intestinal failure, small bowel resection, necrotizing enterocolitis, gastro-schisis/omphalocele, atresias, malrotation, Hirschsprung disease)
3. Anticipated prolonged period of NPO status
4. Prematurity
5. Critical illness/trauma
6. ECMO (extracorporeal membrane oxygenation)
7. Failure to thrive

B. Components of PN

1. Macronutrients
 - a. Amino acids
 - b. Dextrose
 - c. ILE
2. Micronutrients
 - a. Vitamins
 - b. Minerals
 - c. Electrolytes
3. Water/fluid

C. Administration

1. Central venous access device: Preferred route of administration in order to provide optimal nutrition; higher concentrations of macronutrients and micronutrients are possible with central administration
2. Peripheral venous access device (maximum osmolarity of peripheral PN is 900 mOsm/L*)
**Note: Some institutions may set higher maximums (e.g., 1000 mOsm/L).*
3. Typically administered as 2-in-1 PN (all components except for ILE infusion by 1 lumen plus ILE infused separately). 3-in-1 PN typically avoided in hospitalized pediatric patients for the following reasons: lower calcium-phosphorus solubility, inability to visualize particulates, and intravenous incompatibility with other medications. 3-in-1 PN may be used for home-PN patients.
4. Parenteral nutrition must be filtered. The American Society for Parenteral and Enteral Nutrition recommends a 1.2 micron filter for all PN and ILEs.
5. *Note: The American Society for Parenteral and Enteral Nutrition recommends that PN is photoprotected from the time of compounding through administration.*

D. Macronutrients

1. Protein/amino acids
 - a. Crystalline amino acid solutions that provide essential, semi-essential, and nonessential amino acids (e.g., Aminosyn, Premasol, TrophAmine, Travasol, FreAmine)
 - b. Cysteine is conditionally essential during the neonatal period: A dose of 40 mg/g of amino acid may be added to neonatal solutions (additional benefit in lowering solution pH and improving calcium-phosphorus solubility).
 - c. Amino acid provides 4 kcal/g.
2. Carbohydrates/dextrose
 - a. Main source of energy
 - b. Dextrose provides 3.4 kcal/g.
 - c. Measured in DIR (dextrose infusion rate) – Milligrams per kilogram per minute
 - d. DIR gradually increased to goal rates; gradual increase helps prevent hyperglycemia and glycosuria
 - e. Exceeding the maximum DIR may lead to complications (refer to Table 10 and see section X. Safety Considerations/Complications of Parenteral Nutrition).
3. Fat/ILE
 - a. Prevents essential fatty acid deficiency by providing linoleic and α -linolenic acid (minimum soy-oil ILE dose to prevent essential fatty acid deficiency = 0.5–1 g/kg/day)
 - b. Provides 2 kcal/mL (if using 20% solution)
 - c. Total caloric contribution from ILE should not exceed 30%–40% of daily calories.
 - d. Caution should be used in administering to patients with an allergy to peanut, soy, fish, and/or eggs.

Patient Case

10. A 2-month-old previously premature baby (weight 3.4 kg) is receiving continuous PN with the following macronutrients: DIR 14 mg/kg/minute, amino acids 3.2 g/kg/day, and ILE (20%) 3 g/kg/day (51 mL). Which most accurately reflects the infant's caloric intake for the day?
- 111 kcal/kg.
 - 379 kcal/kg.
 - 413 kcal/kg.
 - 130 kcal/kg.

E. Initiation and Advancement of Macronutrients (Table 10)

Table 10. Macronutrients: Initiation, Advancement, and Goals

		Premature Neonate	Term Neonate/Infant	Child	Adolescent/Adult
Initiation	ILE	0.5–1 g/kg/day (max 0.15 g/kg/hr)	0.5–1 g/kg/day	1–2 g/kg/day	1 g/kg/day
	Amino acids	1–4 g/kg/day	2.5–3 g/kg/day	1.5–2.5 g/kg/day	0.8–2 g/kg/day
	Dextrose	6–8 mg/kg/min	6–8 mg/kg/min	3–6 mg/kg/min	2.5–3 mg/kg/min
Advancement	ILE	0.5–1 g/kg/day (max 0.15 g/kg/hr)	0.5–1 g/kg/day	0.5–1 g/kg/day	0.5–1 g/kg/day
	Amino acids	0.5–1 g/kg/day	0.5–1 g/kg/day	0.5–1 g/kg/day	0.5–1 g/kg/day
	Dextrose	1–2 mg/kg/min	1–2 mg/kg/min	1–2 mg/kg/min	1–2 mg/kg/min
Goals	ILE	3 g/kg/day (max 0.15 g/kg/hr)	2.5–3 g/kg/day	2–2.5 g/kg/day	1–2 g/kg/day
	Amino acids	3–4 g/kg/day	2.5–3 g/kg/day	1.5–2.5 g/kg/day	0.8–2 g/kg/day
	Dextrose	10–14 mg/kg/min (max 14–18 mg/kg/min)	10–14 mg/kg/min (max 14–18 mg/kg/min)	8–10 mg/kg/min	5–6 mg/kg/min

ILE = lipid injectable emulsion.

F. Micronutrients

- Electrolytes; added amounts vary according to age, clinical status, and concomitant medications (Table 11 provides typical daily requirements). Optimization of calcium and phosphorus is important, especially in neonates and infants.

Table 11. Electrolytes: Typical Daily Requirements

	Preterm Neonates	Term Neonates	Infants/Children
Sodium	2–5 mEq/kg	2–4 mEq/kg	2–5 mEq/kg
Potassium	2–4 mEq/kg	2–4 mEq/kg	2–4 mEq/kg
Phosphorus ^a	1–2 mmol/kg	0.5–2 mmol/kg	0.5–2 mmol/kg
Magnesium	0.3–0.5 mEq/kg	0.3–0.5 mEq/kg	0.3–0.5 mEq/kg
Calcium ^a	2–4 mEq/kg	2.5–3.5 mEq/kg	0.5–2 mEq/kg

^aCertain Ca:P ratios are required to optimize delivery to prevent metabolic bone disease and clinical outcomes while avoiding precipitation in solution.

2. Vitamins
 - a. Cofactors for many metabolic functions in body
 - b. Provided in PN as fat- and water-soluble vitamins
 - c. Dosing
 - i. Neonates: 2 mL/kg/day; maximum 5 mL/day
 - ii. Infants and children less than or equal to 11 years: 5 mL/day
 - iii. Children greater than 40 kg or greater than 11 years and adults: use adult formulation 10 mL/day
3. Trace elements (copper, chromium, zinc, selenium, manganese)
 - a. Cofactors for many enzymes and crucial functions in body
 - b. Zinc losses may be higher in children with short bowel syndrome through ostomy and diarrhea.
 - c. Recommended dosing (Table 12)

Table 12. Trace Elements: Recommended Daily Dose^a

	Preterm Neonate (< 3 kg)	Term Neonate (3–10 kg)	Infants, Children, and Adolescents (10–40 kg)	Adolescents (> 40 kg)
Chromium ^b	0.05–0.3 mcg/kg	0.2 mcg/kg	0.2 mcg/kg (max 5 mcg/d)	5–15 mcg
Copper	20 mcg/kg	20 mcg/kg	20 mcg/kg (max 500 mcg/d)	200–500 mcg
Manganese ^b	1 mcg/kg	1 mcg/kg	1 mcg/kg (max 55 mcg/d)	40–100 mcg
Selenium	2 mcg/kg	2 mcg/kg	2 mcg/kg (max 100 mcg/d)	40–60 mcg
Zinc	400 mcg/kg	250 mcg/kg	50 mcg/kg (max 500 mcg/d)	2–5 mg

^aNote: Doses of trace elements may require individualization, depending on clinical status. For example, the doses of copper and manganese may require dose adjustment in the setting of cholestasis/liver disorders, and the doses of chromium and selenium may require adjustment in the setting of renal dysfunction.

^bNote: Chromium and manganese are contaminants in intravenous products. Some institutions no longer provide chromium and manganese in parenteral nutrition.

4. Other additives
 - a. Levocarnitine: Cotransports fatty acids across mitochondrial membrane – Doses of 5–20 mg/kg/day. May be added when PN is exclusive source of nutrition for > 4 weeks or when deficiency is present.
 - b. H₂RAs (histamine-2 receptor antagonists) – Reports of association with necrotizing enterocolitis in premature neonates
 - c. Heparin: Dose of 0.5 unit/mL - 1 unit/mL may be added to maintain line patency in low-flowing lines (e.g., less than 10 mL/hr)

X. SAFETY CONSIDERATIONS/COMPLICATIONS OF PARENTERAL NUTRITION

- A. Hypoglycemia/Hyperglycemia
 - 1. Monitoring: Serum glucose concentrations daily
 - 2. Management: Increase or decrease the DIR for hypoglycemia and hyperglycemia, respectively. Insulin is not first-line therapy.
- B. Hypertriglyceridemia
 - 1. Monitoring: Serum triglycerides once or twice weekly
 - 2. Management: Decrease or hold (24–48 hours) ILE infusion for elevated serum triglycerides greater than 200-250 mg/dL (note: typically decrease ILE dose if serum triglycerides less than 400 mg/dL; if greater than 400 mg/dL, hold for 24–48 hours). Levocarnitine may be added to parenteral nutrition.
- C. Acid-Base Disorders and Electrolyte Disturbances
 - 1. Monitoring: Daily serum electrolytes during initiation of PN until stable; then once or twice weekly (in preterm neonates/infants, labs may be done less frequently to conserve blood volume)
 - 2. Management: Adjust chloride and acetate added to PN as indicated.
- D. Refeeding Syndrome: Patients who are very undernourished are at risk
 - 1. Monitoring: Vital signs, serum electrolytes, particularly magnesium, potassium, and phosphorus, trace elements, and vitamins
 - 2. Management: Electrolyte and vitamin replacement (e.g., thiamine, B vitamins, multivitamin), slow initiation of nutrition
- E. Central Line Infection
 - 1. Monitoring: Local signs of infection (e.g., erythema), systemic signs of infection (e.g., fever, positive blood cultures)
 - 2. Most common organism: *Staphylococcus* spp.; however, in children with short bowel syndrome, gram-negative infections are common as a result of intestinal bacterial overgrowth and translocation of microorganisms
 - 3. Management: Removal of central venous access device (if able), chlorhexidine skin preparation, systemic antibiotics, antibiotic lock therapy, ethanol lock therapy*, aseptic technique with line care
**Note: Ethanol lock therapy is incompatible with heparin; therefore, if heparin is a component of parenteral nutrition, care should be taken to avoid incompatibilities.*
- F. Thrombosis
 - 1. Large vessel: Typically associated with central venous access device
 - 2. More common in patients younger than 1 year
 - 3. May require anticoagulation treatment and/or prophylaxis
- G. Metabolic Bone Disease
 - 1. Monitoring: Physical examination, radiography, bone mineral density, serum vitamin D concentration, alkaline phosphatase, intact parathyroid hormone concentration, serum aluminum concentration can be considered
 - 2. Management: Provision of adequate calcium, phosphorus, and vitamin D, reducing/minimizing aluminum in PN

H. Intestinal Failure Associated Liver Disease (IFLAD)

1. Typically diagnosed when direct bilirubin is greater than 2 mg/dL for 2 consecutive weeks in absence of other causes of liver disease (e.g., biliary atresia)
2. Risk factors
 - a. Prolonged administration of PN (more than 2 weeks)
 - b. Low gestational age and birth weight
 - c. Inability to tolerate enteral nutrition/lack of enteral feeding
 - d. Short bowel syndrome/intestinal failure
 - e. Recurrent episodes of sepsis
 - f. Excessive caloric intake
 - g. Administration of certain components of PN, specifically soybean oil-based ILE
3. Approaches to management
 - a. Initiate enteral nutrition when clinically feasible.
 - b. Avoid overfeeding.
 - c. Cycle PN; ideally patient is greater than 5 kg; smaller patients may be unable to tolerate time off.
 - d. Trace element management
 - e. Alternative ILE strategies
 - i. Use of alternative ILEs such as fish oil-based emulsions or Multi-oil component ILEs (i.e., SMOFlipid: soybean oil, medium chain triglycerides, olive oil, fish oil-ILE)
 - ii. Reduce soybean oil-based ILE doses to 1 g/kg/day or less.
 - iii. With either alternative ILEs or reduced-dose fat emulsions, patients should be monitored more closely for essential fatty acid deficiency.
 - f. Use of ursodiol 10 mg/kg/dose every 8 hours (only if patient can tolerate administration of enteral medications)
 - g. If intestinal bacterial overgrowth is present, consider cycled enteral antibiotics with gram negative, anaerobic, and sometimes fungal coverage (note: a variety of regimens are used)

XI. FAILURE TO THRIVE

- A. Weight for Age – Less than 5th percentile on standardized growth charts
- B. Weight for Height – Less than 5th percentile on standardized growth charts
- C. Decreased Growth Velocity – Weight falls by at least 2 major percentile lines on a growth chart in a 6-month period
- D. Types of Malnourished States
 1. Marasmus
 - a. Energy-deficient state
 - b. Generalized muscle wasting and absence of subcutaneous fat
 2. Kwashiorkor – Protein-deficient state
 3. Marasmic-Kwashiorkor – Clinical features of both marasmus and kwashiorkor
- E. Causes
 1. Organic (30%–40%)
 - a. Congenital
 - b. Metabolic
 - c. Immune system
 - d. Medical

2. Inorganic (75%–90%)
 - a. Overfeeding
 - b. Unusual dietary beliefs
 - c. Depression/poverty/isolation
 - d. Hyper-alertness
 - e. History of feeding problems
 - f. Hospitalization
- F. Diagnosis of Failure to Thrive – History
 1. Medical
 2. Feeding
 3. Social
- G. Risk Factors
 1. Low birth weight
 2. Behavior difficulties
 3. Sleeping problems
 4. Elimination problems
 5. Lower socioeconomic status
- H. Assessment
 1. Weight, height, head circumference
 2. Physical appearance, including skin, muscle mass, head, mouth, abdomen, and extremities

Note: Please refer to Section VI.C on nutrition assessment.
- I. Treatment
 1. Hospitalization, if indicated
 2. Investigate and treat underlying etiologies.
 3. Reinitiate enteral nutrition (gradually).
 - a. Watch for refeeding syndrome if severe malnutrition
 - b. Severe hypophosphatemia
 - c. Can lead to congestive heart failure, respiratory distress, peripheral edema
 4. Calorie count
 5. Feeding behavior

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: B

Answer B is correct; the Holliday-Segar method for calculating maintenance intravenous fluids yields $10 \text{ kg} \times 100 \text{ mL/kg/day} + 10 \text{ kg} \times 50 \text{ mL/kg/day} + 15 \text{ kg} \times 20 \text{ mL/kg/day} = 1800 \text{ mL/day}$, which is equivalent to 75 mL/hour. Answers A, C, and D are calculated incorrectly, making them incorrect.

2. Answer: A

Answer A is correct; dextrose 5% in 0.45% sodium chloride plus potassium chloride 20 mEq/L at 75 mL/hour would provide the patient with the following: dextrose at around 2.6 g/kg, sodium at around 4 mEq/kg, and potassium at around 1 mEq/kg. This is within the estimated maintenance needs for pediatric patients. The dextrose 10%-containing fluids (Answers B and D) would provide too much dextrose, and dextrose 5% in 0.225% sodium chloride (Answer C) is a hypotonic fluid that is not appropriate at this age. Of note, if dextrose 5% in 0.9% sodium chloride plus potassium chloride 20 mEq/L were provided as an option, this would also be an acceptable fluid to choose, depending on the clinical scenario. Newer data support consideration of the use of isotonic fluids in hospitalized patients.

3. Answer: B

Answer B is correct; the patient's ongoing loss of bile/gastric fluid is best replaced by 0.9% sodium chloride because of the electrolyte composition of bile/gastric fluid. Of note, although bile does contain 5–15 mEq/L of potassium, many institutions do not allow potassium to be added to replacement fluids for safety reasons. Dextrose is unnecessary when choosing a fluid for replacing losses, and 0.45% sodium chloride does not contain sufficient sodium content to adequately replace the sodium that would be lost in the output of bile (Answers A, C, and D). As a reminder, replacement of ongoing losses should be considered separately from normal maintenance requirements. In clinical practice, replacement fluids are often administered as 0.5 mL per 1 mL of loss or 1 mL for 1 mL of loss.

4. Answer: A

Answer A is correct; the percentage of dehydration is 5% [$\% \text{ dehydration} = (15.8 \text{ kg} - 15 \text{ kg}) / 15.8 \text{ kg} \times 100$]. For a 3-year-old child, this would be classified as moderate dehydration. Answers B and C are incorrect

because of mathematical miscalculation. Answer D is incorrect; for a 3-year-old child, 5% dehydration is considered moderate, whereas 5% would be considered mild if this patient were an infant.

5. Answer: A

Answer A is correct: 0.79 L (790 mL). The fluid deficit is calculated by multiplying the percentage of dehydration by the pre-illness weight. Therefore, $0.05 \times 15.8 \text{ kg} = 0.79 \text{ L}$. Answers B–D are incorrect because of mathematical miscalculations.

6. Answer: D

Answer D is correct. Use of antidiarrheal agents is not recommended during acute episodes of gastroenteritis (Answer C). Similarly, use of sports drinks as oral rehydration for pediatric patients with nausea, vomiting, and/or diarrhea is not recommended (Answer A). Typically, these drinks provide excessive carbohydrates, which can worsen diarrhea. Use of commercially available oral rehydration solutions such as Pedialyte is recommended. For mild dehydration, a dose of 50 mL/kg followed by 10 mL/kg for each stool and/or emesis is recommended. Answer B is incorrect because this would be indicated for more moderate/severe dehydration.

7. Answer: D

Answer D is correct. This patient presents with severe hypotension and is in the emergency phase of intravenous fluid replacement. The most appropriate first-line therapy is administering a 0.9% sodium chloride bolus to reestablish intravascular volume, maintaining hemodynamics, and preventing tissue damage. The most appropriate first-line option is 0.9% sodium chloride or lactated Ringer solution. Answers A and B are incorrect because of the fluid choice. Answer A provides maintenance fluid requirements, but it will not correct the acute phase of resuscitation/restore blood pressure. Answer B is incorrect because it uses maintenance fluids at a bolus dose. When administering a bolus, 0.9% sodium chloride or lactated Ringer solution is more appropriate. Answer C is incorrect; although 92 mL/hour is the maintenance rate needed, the patient requires a bolus for initial therapy.

8. Answer: B

Answer B is correct. With a falling hematocrit value and obvious signs of bleeding, the most appropriate fluid is blood. This will expand the intravascular volume while increasing the hematocrit and oxygen-carrying capacity of the bloodstream. Answer A is incorrect because providing an additional bolus is unlikely to result in efficacy at this point. Answers C and D are incorrect because providing maintenance fluids at 92 mL/hour will not acutely correct the patient's hypotension.

9. Answer: A

Answer A is correct. This patient must consume 320 kcal/day to support normal growth and development. Breast milk provides around 20 kcal per 30 mL. As such, the patient must consume $480 \text{ mL} = 60 \text{ mL}$ per feed. Answers B–D are incorrect because of mathematical miscalculations.

10. Answer: A

Answer A is correct. To solve this question, dextrose and amino acid must first be converted to grams per day: 68.5 g/day and 10.9 g/day, respectively. Then, the caloric contribution from each macronutrient must be calculated: $68.5 \text{ g} \times 3.4 \text{ kcal/g} + 10.9 \text{ g} \times 4 \text{ kcal/g} + 51 \text{ mL} \times 2 \text{ kcal/mL} = 378.5 \text{ kcal/day} = 111 \text{ kcal/kg/day}$. Answers B–D are incorrect because of mathematical miscalculations.

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1. Answer: C

Answer C is correct. Using the Holliday-Segar method for calculating maintenance intravenous fluids, this patient should receive 72.5 mL/hour (maintenance intravenous fluids = $10 \text{ kg} \times 100 \text{ mL/kg/day} + 10 \text{ kg} \times 50 \text{ mL/kg/day} + 12 \text{ kg} \times 20 \text{ mL/kg/day} = 1740 \text{ mL/day} = 72.5 \text{ mL/hour}$). When choosing between Answers C and D, Answer D is incorrect because it will provide greater than maintenance requirements of dextrose. Specifically, dextrose 10% in 0.45% sodium chloride plus potassium chloride 40 mEq/L would provide dextrose 5.3 g/kg/day, which is greater than the 3 g/kg/day needed for maintenance. Answer A is incorrect because the rate of 108 mL/hour is around 1.5 times the maintenance rate, and the fluid choice would provide more dextrose than needed to meet maintenance requirements. Answer B is incorrect because 108 mL/hour is 1.5 times maintenance. Of note, if dextrose 5% in 0.9% sodium chloride plus potassium chloride 20 mEq/L were provided as an option (at the appropriate rate), this would also be acceptable, depending on the clinical scenario. Newer data support considering the use of isotonic fluids in hospitalized patients.

2. Answer: B

This patient's serum creatinine is elevated, which is one sign of ongoing dehydration and a sign that the initial fluid was inadequate. In addition, the patient's serum potassium is elevated to 6.5 mEq/L (normal 3.5–5.5 mEq/L). As such, it is most appropriate to remove potassium from the intravenous fluids at this time, especially because the rate will be increasing. Answer B is correct because the rate of 105 mL/hour is 1.5 times the maintenance rate of 70 mL/hour. Answer A is incorrect because the rate of 165 mL/hour is more than 2 times the maintenance rate and would provide potassium chloride at 1.2 mEq/kg/day, which is not clinically warranted with a serum potassium of 6.5 mEq/L. Answer C is incorrect because dextrose 10% would provide too much glucose, and potassium is not needed at this time. Answer D is incorrect because dextrose 10% would provide too much glucose, and potassium is not needed at this time; further, the rate of 165 mL/hour is incorrect.

3. Answer: C

The patient presents with a severe intravascular deficit, as evidenced by her hypotension and disorientation. During the emergency phase of resuscitation, the most appropriate first-line therapy is a 0.9% sodium chloride bolus at a dose of 10–20 mL/kg. This will restore intravascular volume and perfusion, making Answer C correct. Although providing albumin and blood (colloids) might be useful, these would not be first-line therapies without a clear source of bleeding. In addition, when volume expansion is desired, 5%, rather than 25%, albumin should be used, making Answer A incorrect. Furthermore, the dose of albumin provided in Answer D is above what would typically be indicated, making Answer D incorrect. Answer B provides maintenance fluids. For severe hypotension, intravascular volume must first be restored with a bolus, making Answer B incorrect.

4. Answer: D

Answer D is correct. This patient has not responded to the 0.9% sodium chloride bolus that was given in the ED, and now, she has a clear sign of intra-abdominal bleeding. Administering blood will expand the intravascular volume while increasing hematocrit and the oxygen-carrying capacity of the blood, which is necessary to continue perfusing vital organs, especially during an acute trauma. Answer A is incorrect because there is now a clear source of bleeding. In addition, a dose of 10 mL/kg in the setting of severe hypotension would be insufficient to restore intravascular volume. Answer B is incorrect; this maintenance fluid would be needed after correcting the acute phase of dehydration. Answer C is incorrect; simply increasing the volume of the 0.9% sodium chloride bolus will not help correct this acute issue because there is now a clear source of bleeding.

5. Answer: B

Answer B is correct. The percentage of dehydration is calculated as 4.3% [$\% \text{ dehydration} = (10.45 \text{ kg} - 10 \text{ kg})/10.45 \text{ kg} \times 100 = 4.3\%$]. Therefore, this patient would be classified as having moderate dehydration (i.e., 4%–6% dehydration for children). Signs and symptoms typically associated with moderate dehydration include slightly increased heart rate, normal-low systolic blood pressure, markedly decreased urinary output, dry

mucosa, reduced tears, deep-set eyes, decreased skin turgor, cool skin, reduced fontanelle, capillary refill of greater than 5 seconds, and irritability. Answer A is incorrect because these symptoms would be more consistent with severe dehydration. Answer C is incorrect because these symptoms would be more consistent with mild dehydration. Answer D is incorrect because the symptoms of dehydration are mixed between mild, moderate, and severe.

6. Answer: A

Answer A is correct. Given the 4.3% dehydration, this patient's fluid deficit is around 450 mL (fluid deficit = $4.3\% \times 10.45 \text{ kg}/100 = 449 \text{ mL}$). In addition, using the Holliday-Segar method for maintenance needs, the patient requires 1023 mL/day for maintenance. The most appropriate way to administer this is to provide one-half of the deficit over the first 8 hours and one-half over the next 16 hours. Likewise, the maintenance needs should be replaced by one-third over the first 8 hours and by two-thirds over the next 16 hours. Answer B is incorrect because this would only replace the deficit; it would not also provide maintenance requirements. Answer C is incorrect because a bolus is not indicated at this time (i.e., blood pressure is stable). In addition, this patient will require maintenance fluids for 24 hours, not 16. Answer D is incorrect because a bolus is not currently indicated (i.e., blood pressure is stable).

7. Answer: A

Answer A is correct. Because the patient is a term infant who will receive standard enteral formula, Enfamil is most appropriate. Enfamil is 20 kcal/oz, as are most standard infant formulas. Because this patient will require about 100 kcal/kg/day to support adequate growth and development (20–30 g/day), he will require formula at 570 mL/day. Most term neonates will feed about every 3 hours; therefore, a volume of 72 mL every 3 hours will provide the nutritional support needed. Answer B is incorrect because Similac Special Care Advance 24 is a more calorically dense formula than is used for premature neonates. Answer C is incorrect because Enfaport is a special formula consisting of medium-chain fatty acids used for patients with chyllothorax or chyle leaks. Answer D is incorrect because Similac PM 60/40 is a specialty formula used for infants with renal or cardiovascular problems.

8. Answer: C

Answer C is correct. Elevated bilirubin greater than 2 mg/dL in PN-dependent children is most likely caused by IFALD. The exact cause of IFALD is unknown; however, it is multifactorial and associated with prolonged use, lack of enteral nutrition, recurrent episodes of infection/sepsis, and low birth weight/gestational age. Although many of these factors depend on one another, an independent risk factor for developing IFALD is the administration of soybean oil-based ILE because of the presence of proinflammatory mediators, phytosterols, and omega-6 fatty acids. Although this has not been conclusively determined, expert consensus agrees that reducing soybean oil-based ILE to doses of 1 g/kg/day or less may prevent and/or treat IFALD. An alternative approach is to switch to FO-ILE at a dose of 1 g/kg/day. Answer A is incorrect because this patient is PN-dependent (i.e., short bowel syndrome); further, holding PN for 48 hours will unlikely normalize direct bilirubin/IFALD. Answer B is incorrect because cysteine is added to neonatal PN to increase the calcium-phosphorus solubility. Answer D is incorrect because heparin is added to neonatal PN solutions to maintain line patency.

9. Answer: B

Answer B is correct; ILE at 20% provides 2 kcal/mL, amino acids provide 4 kcal/g, and dextrose provides 3.4 kcal/g. As such, the total caloric provision of this particular PN regimen is as follows: $(12 \text{ mL} \times 2 \text{ kcal/mL}) + (7.8 \text{ g} \times 4 \text{ kcal/g} + 46.4 \text{ g} \times 3.4 \text{ kcal/g}) = 213 \text{ kcal}$. Then, accounting for the child's weight, the total kilocalories per kilogram provided is 93 kcal/kg. Answer A is incorrect because it fails to account for the child's weight, providing the total calories provided instead of the kilocalories per kilogram. Answers C and D are incorrect; each answer uses incorrect values to calculate calories, specifically: $(12 \text{ mL} \times 2 \text{ kcal/mL}) + (2.6 \times 4 \text{ kcal/g}) + (15.5 \times 3.4 \text{ kcal/g}) = 87$ for Answer D and, for Answer C, $87 \times 2.3 = 200$. Both options are incorrect and fail to use the total grams of amino acid and dextrose in the calculation.

10. Answer: B

Answer B is correct. The DIR is measured in milligrams per kilogram per minute. The DIR in this question can be calculated in two ways:

$28.7 \text{ g} \times 1000 \text{ mg/g} = 28,700 \text{ mg/day} \div 1440 \text{ minutes/day} \div 1.535 \text{ kg} = 13 \text{ mg/kg/minute}$, OR

$21.4 \text{ g/100 mL} \times 5.6 \text{ mL/hour} \times 1000 \text{ mg} \div 60 \text{ minutes} \div 1.535 \text{ kg} = 13 \text{ mg/kg/minute}$

Because of mathematical miscalculations, Answers A, C, and D are incorrect.

11. Answer: C

Answer C is correct. There are several risk factors for failure to thrive; in this case, the patient's low birth weight because of prematurity is the most likely cause. Although the patient has gastroesophageal reflux, his case is mild; therefore, Answer D is incorrect. Although severe gastroesophageal reflux may be a cause of failure to thrive, this is unlikely the main causative factor in mild cases. Answer A is incorrect because early hospitalization alone has not been linked to failure to thrive. Answer B is incorrect because the patient probably does not have an undiagnosed metabolic disorder, given that he has gained weight during the first 7 months of life, despite being below the 5th percentile. Moreover, metabolic disorders would likely be diagnosed earlier and are rare.

12. Answer: A

Answer A is correct. The maximum osmolarity for PN infused through a peripheral venous access device is 900 mOsm/L. Parenteral nutrition above this must be infused through a central venous access device to prevent phlebitis, making Answers B–D incorrect.

13. Answer: B

It is most appropriate to administer PN to this patient right now. Pediatric patients with pure esophageal atresia cannot ingest nutrition by the oral route initially and must wait until surgical repair or until gastric or jejunal access is secured. Furthermore, Answers A and D are incorrect because of the choice of enteral formula. Even if this patient could be fed enterally, a standard premature enteral formula would be better. Of the two PN regimens provided, Answer B is correct for initiation. Dextrose and ILE are initiated at a low dose and titrated slowly toward goal calories. Answer C is inappropriate for initial PN therapy because of the percentage of dextrose as well as the ILE dose.



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